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CONTENTS

Foreword

One of the great economic developments in the field of antibiotics is the use of these drugs in feeds for the promotion of animal growth. During the past few years there has been a steady increase in the amount of antibiotics — largely penicillin, chlortetracycline oxytetracycline, and bacitracin — used for this purpose. In 1954 alone, some 490 000 pounds of these drugs were incorporated into feeds rendering the farmer tremendous savings. Because antibiotics stimulate the growth of swine, chicks, and poults, they cut down the feed consumption of these animals, since they can be sent to slaughter much sooner and in a healthier condition than they would have been prior to the use of these drugs.

A unique phenomenon — perhaps without precedent in the history of medicine — is indeed the present use of the so-called antibiotics as stimulants of growth and nutrition in both human beings and animals.

The opposite phenomenon has already been recorded in history namely the use of such nutritive elements as vitamins, mineral salts, and amino acids as therapeutic agents. Vitamins were known and developed primarily as a component of the normal diet of human beings and animals only recently were they synthesized and developed as powerful therapeutic drugs. But never before has a medicinal drug been used in animal feeding or in the diet of humans to stimulate nutrition and promote the speed and extent of growth.

This new application for antibiotics will surely not only greatly widen the horizon of their usefulness, but also markedly affect the nutritional and economic problems of the world probably so much so that antibiotics may in the future become a most valuable element in solving the ever-growing disproportion between increasing world population and food supplies.

The use of antibiotics in nutrition has also opened up new avenues for research into such basic philosophical problems of biology as the influence of environmental bacteria on animal growth the correlation between the biochemical action of antibiotics and the anatomical changes in the morphology of animals fed with these substances the philosophical question of "germ free" animal life versus the growth of animals whose bodies, as well as their environment, are literally soaked in bacteria, and finally the correlation between the prolonged administration of antibiotics to animals and their vitamin and mineral requirements.

These and other vital problems will eventually be solved thanks to the searching light projected by antibiotics and antibiotic research upon the field of nutrition.

We were indeed fortunate that Dr Thomas H. Jukes prepared the monograph on "Antibiotics in Nutrition." This is the fourth in the monograph series designed to embrace the principal antibiotics and their application, not only in clinical medicine but in other allied fields of usefulness as well. Doctor Jukes is a pioneer in this field. He, together with his colleagues, was the first to demonstrate the effectiveness of chlortetracycline in stimulating the growth of chickens.

In the preparation of this monograph, Dr Jukes has completely covered the development of the use of antibiotics in nutrition. Following a brief introduction in Chapter I, he discusses in some detail the mechanism of the antibiotic growth effect. He covers the effect of feeding antibiotics on the requirement for other nutrients in Chapter III. Chapters IV and V explain the use of antibiotics in animal production and the physiological and other effects of dietary antibiotics A bibliography of more than 400 references is testimony to the thoroughness with which Dr Jukes has covered the subject of antibiotics in animal nutrition. All of the studies done to date concerning the antibiotic effect on the growth of human subjects, are

also included, and the public health aspects of feeding antibiotics to animals is explored.

The correlation of this large mass of data has been a monumental task, but it is so well done that this monograph will be of great value to public health and research workers veterinarians, economic specialists, and those interested in the impact of the ever widening use of antibiotics in our daily life

Doctor Jukes has written his monograph in a clear terse, easily readable style We consider it a very worthwhile and valuable addition to this series

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"Often in our laboratory discussions for the last several years I have told the young research workers in my group that there should be much interest in raising young animals such as rabbits, guinea pigs, dogs and chicks from birth on pure food materials. By this latter expression I refer to food products which have been freed completely from common microbes by laboratory methods. Without wishing to speak positively I wish to state that I would undertake this investigation if I had time with the expectation that life under these conditions would become impossible. By such an approach one could perhaps attempt to study the digestive process by the systematic addition of microbe-free nutritive materials or single strains of microbes or mixed cultures of known microbes. The egg of the chicken lends itself without serious difficulty to this type of experiment. The outside of the shell could be kept free from bacteria at the moment the chick hatched and then the chick could be placed in a germ free environment ventilated by sterile air and sterile food (water milk and grains) could readily be introduced from the outside.

"Whether the result would be positive and would confirm the preconceived idea which I have put forward or whether it would be negative or even reversed, that is to say that life under these conditions would be actually stimulated, it would be of great interest to try such an experiment."

(Pasteur, L., as quoted by Duclaux, E.,
Comptes rendus Volume 100, page 68, 1885)

CHAPTER I Introduction

The use of antibiotics in the control of harmful bacteria is a culmination of years of searching for what has been aptly termed a "magic bullet"[1] a substance that will kill a parasite without harming its host. Antibiotics when added to the food of animals are able to improve their nutrition by producing changes in the intestinal bacteria. This effect was discovered accidentally: the "magic bullet" reached an unseen target. The growth rate of young chickens was found to be increased by adding streptomycin,[2] chlortetracycline,[3] or chlortetracycline fermentation residues[4, 5] to their diet. The work with chlortetracycline residues led promptly to studies with other species and it was found, perhaps not unexpectedly, that the growth promoting effect was even more marked when certain intestinal infections were present. It is now well established that the growth rate of young animals is usually increased by adding relatively small amounts of certain antibiotics to the diet. This effect on growth occurs in apparently healthy animals on diets that are adequate in all known nutritional factors and the effect is also observed on certain deficient diets.

Many antibiotics are toxic to animals but there are certain outstanding and familiar exceptions, which include three antibiotics that are widely used in animal feeds: chlortetracycline,* oxytetracycline,† and penicillin.[6] These three substances are well known for their effectiveness in animals against many disease-producing bacteria and for the absence of harmful effects produced by their use in therapeutic doses. They are commonly used in animal feeds, and bacitracin is used to some extent. These four antibiotics together with streptomycin have been used in many experimental nutritional studies since 1950 and this

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* The trade name of Lederle Laboratories Division, American Cyanamid Co., for chlortetracycline is Aureomycin.

† The trade name of Chas. Pfizer & Co., for oxytetracycline is Terramycin.

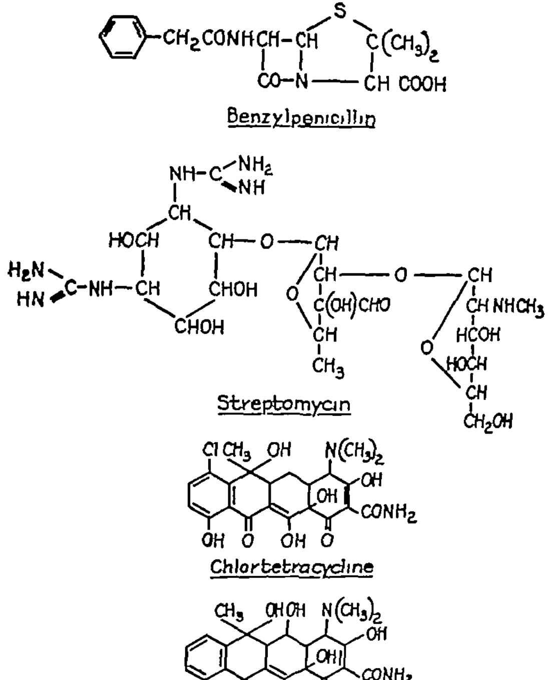
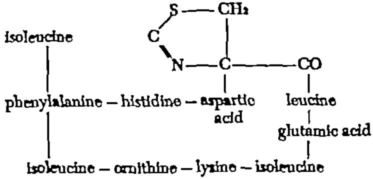


FIG. 1. Structural formulas of penicillin G (benzylpenicillin) streptomycin, chlortetracycline, and oxytetracycline.

monograph will be largely concerned with a review of these studies. The structural formulas of chlortetracycline, oxytetracycline, streptomycin, and penicillin are shown in figure 1 Their distinctive structural chemistry excites interest in the biochemical mechanism by which such widely differing substances inhibit bacterial growth while not injuring the host to which they are administered. The other antibiotic that is used as a supplement to feeds, bacitracin is a mixture of complex polypeptides. Bacitracin A has recently been reported by Craig and co-workers to have the structure



It is nephrotoxic when injected[7] but appears to be absorbed very poorly from the gastrointestinal tract.

The antibiotics are a group of soluble organic substances that are produced by microorganisms and that are characterized by their property of inhibiting at low concentrations the growth, activity or multiplication of other microorganisms Antibiotic like substances are also produced by the flowering plants and by animals Such plants as garlic, hops, and tomatoes contain antibacterial compounds termed respectively "alliine, "lupulon, and "tomatine," while lysozyme, a protein with antibacterial properties, is present in egg white and in the secretions of the eye These substances are not included among the antibiotics because the definition of this term is restricted to compounds that are produced by microorganisms. However the extensive occurrence of antibacterial substances in more complex organisms serves to emphasize their widespread nature. This is a useful reminder of the fact that the introduction of small quantities of antibiotics into the diet of animals is not necessarily an entirely novel procedure.

The discovery and development of the useful antibiotics have been based on empirical screening procedures that were designed to find an antibacterial substance that was harmless to animals It may be presumed that such a substance must block certain essential enzyme systems in the bacterial cell without appreciably affecting any of the essential systems in the cells of the host. The

mechanism of this biochemical selectivity has been studied from various stand points[8, 9] There may be differences in the biochemical mechanisms of bacteria as compared with animals so that it is possible to block the metabolism of a pathogenic microorganism without harming the host, or there may be differ ences in permeability so that an injurious substance can enter the bacterial cell but not the cells of the host.

Penicillin has been reported to exert its toxic effects on microorganisms only under conditions where their growth is possible.[10] Gale[9] found that penicillin inhibited the formation of combined glutamate in *Staphylococcus aureus* cells while peptide glutamate accumulated in the medium. Bacitracin was found to behave similarly to penicillin.[11] In contrast, chlortetracycline and chloramphenicol tended to inhibit the formation of the peptide rather than the uptake of glutamate.[12] Penicillin has also been found to produce changes in the metabolism of nucleic acid.[13] Streptomycin appears to inhibit the oxaloacetate-pyruvate condensation in *Escherichia coli* and Umbreit et al[14] have suggested that animal cells are not similarly affected because they are less permeable to the antibiotic. Other biochemical reactions in the bacterial cells were unaf fected even by high concentrations of streptomycin.

It is evident from these and other examples that differences between the antibiotics exist with respect to their antibacterial mechanisms as well as to their chemical structures. The only known biochemical property common to the antibiotics under consideration is their antibacterial effect. They do not, for example, all possess a single and distinctive chemical group, which might have a growth promoting effect on animals. The strong inference is that any such effect is secondary to the antibacterial action of antibiotics on the microorganisms in the digestive tract.

Before the discovery of the growth-promoting effect of antibiotics on animals, many investigations were made of the results produced by adding sulfonamides to purified diets It was found that under such conditions deficiencies of biotin, folic acid, and vitamin K were produced.[15-19] However these deficiencies did not appear when these three substances were added to purified diets or when rats received diets of natural foods to which sulfonamides were added. The results were taken to indicate that rats were able to obtain a supply of biotin, folic acid, and vitamin K from a nondietary source when the rats were maintained on a purified diet that was deficient in these three vitamins and that this nondietary source originated in a bacterial fermentation that took place in the intestinal tract. It could be deduced that sulfonamides could depress or change the intestinal bacteria in a manner that interfered with the production of these vitamins, which are needed by the host animal. However

the sulfonamides do not interfere with the assimilation of vitamins that are added to the diet. The reason that deficiencies of biotin folic acid, and vitamin K developed was because they were not added to purified diets for rats, since deficiencies of these vitamins had not appeared before sulfonamides were added. In contrast, thiamine riboflavin, pyridoxine and pantothenic acid were added to the diets because if these additions were not made deficiencies developed even in the absence of sulfonamides.

The concept of a symbiotic relationship between animals and the bacteria in their gastrointestinal tract is an old one. The studies with rats on diets with sulfonamides emphasized this relationship and experiments with ruminants showed that these animals were even more versatile, for it was found that they could largely dispense with certain water-soluble vitamins, which were shown to be produced by fermentation in the rumen [20] Furthermore simple nitrogenous compounds such as urea, can be transformed by the rumen microorganisms into amino acids, which could replace part of the protein requirement of ruminants.

In contrast with these beneficial activities of the microorganisms of the digestive tract, there are many familiar examples of pathogenic bacteria and protozoa that can invade the alimentary canal to produce clinical disease The sulfonamides and antibiotics have made some of their greatest contributions to medicine in controlling enteric diseases produced by organisms of this type

A few investigators in the 1940's described experiments with rats and chicks in which antibacterial substances produced increases in the growth rate of the animals. Martin[21] found that the mortality of young rats was prevented and their growth rate was increased by feeding 1 mg of sulfanilamide daily but it was not clear whether an infection was present. Moore and co-workers[2] found that succinylsulfathiazole and streptomycin increased the growth of chicks on a purified diet. These authors made the important suggestion that the dietary supplements inhibited intestinal bacteria that were producing toxic materials or were *rendering certain dietary vitamins unavailable to the animal*, but that the possibility that the agents were acting systemically could not be overlooked. Morehouse and Mayfield[22] found that 3-nitro-4-hydroxyphenylarsonic acid increased the growth of chicks and turkeys when added to natural diets. This observation was made during studies of the coccidiostatic effect of this substance. A pharmacologic study of chlortetracycline by Harned and coworkers[3] led to an observation that the addition of this antibiotic to the diet increased the growth rate of chicks The effect was attributed to the elimination of some infection. All these studies in which the growth rate of animals was improved by antibacterial substances appeared to indicate that the effect was

due to suppression of harmful microorganisms, and indeed such an effect would not be surprising in view of the association of weight loss with clinical disease. Nevertheless, the possibility had been suggested by Moore and co-workers[8] that unidentified intestinal bacteria could have an inhibitory effect upon growth without causing clinical disease.

Investigations in our laboratory which were first reported in 1949[4,5] showed that a growth-promoting effect was produced in chicks when crude preparations of *Streptomyces aureofaciens* cultures were added to the diet. These experiments were carried out with chicks that were being used to assay the vitamin B_{12} content of *S. aureofaciens* fermentations. The chicks were apparently healthy and were kept in cages that were frequently cleaned. Furthermore, the cages were sterilized with steam at four week intervals. Even with these precautions, the crude fermentation materials containing chlortetracycline produced more rapid growth than could be obtained with crystalline vitamin B_{12} or liver extract. Samples of the fermentation materials, which had been examined in the chick growth test and had been found to contain the new growth factor were sent early in 1949 to other investigators including Catron, Couch, Cunha, Krider McGinnis, and Stugsen, who confirmed the observations during the summer of 1949 and who also showed that other species, such as turkeys and pigs, showed a marked growth response to the fermentation materials. The response was then found to be due to the presence of chlortetracycline in the fermentation materials.[23] Unexpectedly small amounts of chlortetracycline and other antibiotics were found to produce an effect on growth.[24-27] These amounts were so small, 5 to 10 parts per million of diet, that it was economically feasible to incorporate them in commercial diets for farm animals.

The nature and mechanism of the growth-promoting effect produced in young animals by antibiotics has excited the interest and attention of many investigators and some of their findings will be discussed in succeeding chapters.

CHAPTER II Mechanism of the Antibiotic Growth Effect

The action of antibiotics in increasing the growth rate of young animals may be termed for convenience the "antibiotic growth effect. The most obvious explanation of the effect is to postulate that it is due to the action of antibiotics on the intestinal bacteria. In support of this are the following observations

1. A number of different antibiotics will produce the effect on growth but they have no special chemical properties in common Furthermore, their anti bacterial effects are exerted through different mechanisms It is therefore un likely that these antibiotics would all have a stimulatory effect on animal cells and it is much more probable that the effect on growth is secondary to changes in the intestinal bacteria, since many of these bacteria are known to be sus ceptible to the common antibiotics.

2. There have been many observations that the antibiotic growth effect may diminish or disappear entirely when steps are taken to keep bacteria away from the animals. Exceptions to these findings have been noted. However if the growth effect is due to the direct effect of the antibiotic upon the animals, it should be consistently obtainable in clean surroundings which is not the case.

3. Very little is known of the normal effects of the intestinal bacteria on the nutrition of the host animal. For example, it has been shown that feeding antibiotics brings about an increase in the storage of vitamin A in the liver[28, 29] and that a similar increase takes place when the animals are placed in a highly sanitary environment without antibiotics.[30] This may imply that the effect on Vitamin A is secondary to changes in the gut wall, which the antibiotic has produced by its action on the intestinal microflora, indeed, such findings may be a clue to hitherto unrecognized biochemical activities of the intestinal bacteria.

4. The growth-promoting effects of certain antibiotics when injected may be due to their excretion into the intestine This has been shown to occur in

calves under conditions where growth was improved following
of chlortetracycline.[31]

5. The antibiotic growth effect can be produced by certain an
do not readily enter the blood stream when given by mouth. T
streptomycin[32] and bacitracin.[33] It is of interest that bacitracin has
to produce a growth response in chicks when added to the diet[34] b
implanted subcutaneously[35] for injected bacitracin has been rep
excreted in the urine[36] rather than the bile so that it is possible tha
bacitracin may not reach the intestine. In contrast, such antibioti
tetracycline and penicillin, which have been found to produce
sponses when injected,[31, 37, 38] are known to be excreted into the
the bile.[31, 39]

6. A large number of investigations have shown that antibiotic
requirement for certain B vitamins in animals on diets deficient in
mins. The B vitamins differ from each other with respect to their ch
physiology but they share the common property of being produ
intestinal bacteria, and there are indications that antibiotic-toleran
these bacteria will produce increased amounts of B vitamins.[40]

7 Antibiotics disappear rapidly from the tissues of animals
administration is stopped.[41] However under certain experimental
the dietary effect of antibiotics in sparing vitamin B_{12} may persist
after their withdrawal from the diet,[42] thus suggesting that a firmly
change in the intestinal flora has taken place.

8. Several investigators have reported that the growth of unsup
animals gradually tends to improve from experiment to experiment
where other animals are receiving antibiotics, indicating the elim
certain harmful bacteria from the environment.

9 No growth effect was found when antibiotics were injected
ing chick embryos[43] or were fed to germ free chicks[44] at levels that
the growth rate of "contaminated" animals.

10 The beneficial effect of antibiotics on dietary liver necrosis in
to disappear after several weeks of feeding, suggesting that the in
was due to a change in the intestinal flora, which later became toler
antibiotic so that the change was reversed.[45]

The Influence of Environmental Bacteria on the Growth of Animals

The effect of antibiotics in improving growth of animals led to th

sion that bacteria that inhibited growth might be normally present in the intestinal tract. If this assumption were correct, the inhibitory effect should be absent in animals that are free from bacteria, and such animals should not show a growth response to antibiotics. Evidence to test the assumption was sought from several approaches from the concept of "disease level," from comparing animals in "clean" and heavily contaminated surroundings, from measuring the growth of chick embryos, and from studying "germ free" chicks and turkeys.

The Disease Level Concept Experiments with *S aureofaciens* fermentation products in the diets of swine were carried out in 1949 and 1950 by a number of investigators including Cunha et al,[46] Catron,[47] Terrill and Krider[48] and Carpenter[27] Striking effects were noted in the control of diarrhea and in the improvement of growth In many herds, bloody diarrhea was endemic and yielded to treatment with the antibiotic supplement so that the affliction largely disappeared and growth was markedly increased. These observations led to an emphasis by various investigators on the postulation that the antibiotic growth effect in pigs varied with the disease level,[47, 50, 51] a term that was first introduced by Catron,[47] which he has defined as the degree or amount of feed lot contamination with bacteria or virus infestation that causes pigs to scour[48] The definition could probably be extended to include other species of animals in addition to pigs and other pathologic manifestations in addition to diarrhea. This proposal is now well substantiated and it is supported by observations on other farm animals, such as turkeys, chickens, and calves It seems evident that certain subacute infections can often occur in young animals and that these infections are accompanied by slow growth and often by diarrhea. Certain antibiotics will relieve these conditions when added to the diet so that a marked increase in growth rate is observed when antibiotics are administered. However it is also evident that a somewhat less marked effect of antibiotics on growth can be produced in animals that appear to be healthy as judged by a complete absence of external clinical signs It is not clear whether the growth promoting effect of antibiotics on these apparently healthy animals differs only qualitatively from the effect of antibiotics on the growth of animals that are suffering from frank infections However the preponderance of evidence is that both phenomena are part of the same picture and the effect of antibiotics in both cases is to eliminate harmful bacteria.

Relation of Clean and Dirty Environments to the Antibiotic Growth Effect The finding that a high disease level magnified the antibiotic growth effect in pigs leads to the possibility that the effect may disappear in animals if the bacterial contamination of the environment is kept low A report by Coates and

to initiate the proliferation of a thriving and abundant microflora. Taken as a whole, the findings demonstrate that under some sanitary conditions, and perhaps by chance, it is possible to stop certain antibiotic-susceptible and growth-depressing microorganisms from becoming established in the intestinal tract of experimental animals. This is shown by the fact that these animals may grow as well without as with antibiotic supplementation until an outside source of infection is introduced. However the random tendency of natural contamination can lead to a different result so that animals that are kept scrupulously clean may nevertheless acquire and harbor a microflora whose growth-depressing action is eliminated by feeding an antibiotic. The experimental findings in which antibiotics were fed to animals in clean and dirty environments have led to the conclusion that the antibiotic growth effect may be due to the suppression of a growth-depressing microflora that is usually present in healthy animals but that may sometimes be absent under special sanitary conditions.

Antibiotics and the Growth of Chick Embryos The developing chick embryo grows rapidly in the absence of an intestinal flora and its weight increases twenty-six fold during the period between the seventh and seventeenth days of incubation.[43] This is a greater rate of increase than takes place at any time after hatching We concluded that a living organism whose tissues were prolif

Table III

Weight of Chick Embryos at 17 Days as Affected by Injections of Antibiotics

Antibiotic*	Amount Injected, mg	Survival ratio	Average weight	
			Whole egg, Gm.	Embryo Gm.
Chlortetracycline	1.2	19:30	54.1	12.0
Penicillin	1.2	20:30	53.7	12.6
	6.0	22:30	53.6	10.4
Streptomycin	1.2	20:30	54.6	12.5
	6.0	23:30	54.2	12.2
None (distilled water)		26:36	53.7	13.3

The antibiotic was divided into three equal doses, which were injected on three successive days.

erating so rapidly might be unusually sensitive to the effects of a growth-stimulating substance. Accordingly chicken eggs containing living embryos were injected with sterile solutions of antibiotics and the incubation period was continued. The injections were started on the seventh day and on the seventeenth day the embryos were separated from the membranes and weighed.[64] No growth-promoting effect of the antibiotics was found, and no evidence of toxicity as judged by deformities or depression of growth was observed except that the embryos on the higher level of penicillin were somewhat smaller than the others (table III) The results indicated that the antibiotics tested did not increase the growth rate of embryonic tissue and the observation helps to support the idea that the antibiotic growth effect is exerted through the intestinal flora, since these are absent from the developing chick embryo Lepine and co-workers[65] found that slight but consistent diminutions in the proliferation of chick embryo heart and lung fibroblasts and epithelial cells in vitro were caused by chloramphenicol or chlortetracycline, 10 μg./ml. of culture medium. Higher levels of the antibiotics produced marked inhibitory effects on the growth of these tissue cultures. In experiments with brain tissue, 10 μg./ml. of chloramphenicol and 100 μg./ml. of chloramphenicol or chlortetracycline inhibited cell migration while 10 μg./ml. of chlortetracycline had no effect.

Morphologic Changes Produced by Feeding Antibiotics

Gordon[66] made a number of comparisons of the morphology of germ-free chicks with chicks exposed to ordinary contamination, with and without antibiotic feeding Penicillin and oxytetracycline were the antibiotics that were used. A marked reduction, 33 to 50 per cent, of the weights of the small intestine was noted in the germ free animals and in the antibiotic fed conventional animals, by comparison with the conventional nonantibiotic-fed animals. Simultaneously there was a less marked increase in the weight of the thymus gland. No difference between the antibiotic-fed and nonantibiotic-fed germ-free animals was observed with respect to the weights of these organs. The author concluded that antibiotics created "germ-free-like conditions in the conventional animals

It is indeed striking that without reducing the total bacterial count in the intestine of chicks the antibiotics will produce morphologic conditions similar to those in germ-free animals. This observation points strongly to the probability that antibiotic-sensitive bacteria, which produce a tissue reaction, are normally present in the digestive tract.

Table V

Summary of Results with Germ-free Animals in which the Weights at 4 weeks with and without Antibiotic Supplementation Were Compared

Antibiotic	Level per Kg of diet mg	Animals	No. of experiments showing Increased wt	Decreased wt.
Streptomycin	45	Chicks	0	1
Streptomycin	70	Chicks	1	0
Penicillin	11	Chicks	1	0
Penicillin	11	Turkeys	1	0
Penicillin	46	Chicks	1	1
Penicillin	46	Turkeys	3	2
Oxytetracycline	25	Chicks	3	0
Oxytetracycline	25	Turkeys	0	1
Oxytetracycline	50	Chicks	1	3

Taken Luckey and co-workers[44, 71]

somewhat variable but the over-all experience with these two drugs indicated a negative response. The levels of antibiotics in the diet ranged from 23 mg. of chloramphenicol to 50 mg of oxytetracycline per Kg. of diet and the number of chicks per experimental group was necessarily small, ranging from 2 to 6. Similar results were obtained with turkeys which received 50 mg. of penicillin per Kg. of diet so that the author concluded that "no stimulation is seen when germ-free birds are fed antibiotics."

More recently Luckey[71] found that in three out of four experiments with a lower level of oxytetracycline, 25 mg./Kg. of diet, the birds receiving the antibiotic grew more rapidly than the unsupplemented birds and slight increases in the growth rate, 3 to 7 per cent greater than the controls, were noted in two experiments in which a lower level of penicillin, 11 mg /Kg. of diet, was fed while in three experiments with turkeys receiving 46 mg. of penicillin per Kg of diet, the weights of the supplemented birds were respectively 1, 7 and 13 per cent higher than those of the controls. He inferred that the difference between these and the earlier results was that the levels of oxytetracycline

and penicillin used in 1952 were higher and therefore growth-depressing However the small number of birds involved and the great variability in the individual weights make it impossible to arrive at a definite conclusion that a growth effect was observed at these lower levels of antibiotics It seems unlikely that levels of 50 mg of oxytetracycline or penicillin would have a specific depressing effect on the growth of germ free birds when much higher levels of these antibiotics do not slow the growth of birds under ordinary conditions. The variability encountered in these experiments may be seen in table IV in which the weights of all the germ-free birds receiving oxytetracycline as described by Luckey are summarized.

A condensed summary of the results described in Luckey's two communications on antibiotics and the growth of germ free birds is given in table V Table V shows that the antibiotic-fed birds were heavier than the controls at 4 weeks in 11 of the 19 experiments. This would seem to lead to the conclusion that there was about an equal chance of the antibiotics increasing or decreasing growth, and the over-all result appears to confirm the conclusion reached by Luckey in 1952.

Effects on Intestinal Flora

Many studies have been made of the bacteriology of the intestinal contents of animals fed antibiotics in efforts to throw some light upon the antibiotic growth effect. The results have varied greatly and Sieburth and co-workers[72] pointed out that variations may be due to different basal diets, different bacteriologic procedures, the age of the birds studied and the types and levels of antibiotics used. Furthermore, their investigations showed that extreme variations in the cecal and fecal microflora were found even from day to day

Examples of the differences noted by various investigators may be seen in table VI. These differences are so numerous that we hesitate to review the literature in detail or to attempt to draw generalizations with respect to the various bacterial types Thus Kratzer and co-workers[73] found a five- to ten fold increase in the number of yeasts in the excreta of chicks and turkey poults fed streptomycin, while Williams and co-workers[74] found little or no change in the yeast count of chicks fed chlortetracycline Sieburth and co-workers[75] drew attention to the marked reduction in intestinal clostridia produced by feeding antibiotics and this was confirmed by Elam and co-workers[76] and by Williams and co-workers[74] However Williams and co-workers found that feeding live cultures of hemolytic toxin producing clostridia did not reduce the growth of chicks that were not receiving antibiotics, and no growth-depressing effect was

found when cell-free clostridia toxins were fed to unsupplemented contr[ol] chicks fed antibiotics. Elam and co-workers[78] found that feeding fecal clostri[dia] depressed the growth of chicks in clean quarters but not in old quarters. In [a] later communication, Sieburth and co-workers[73] concluded that little signifi-cance could be attached to the observation that the toxin-producing clostridia are greatly reduced by antibiotic supplementation, because the population of these organisms is small in comparison with other types. These authors noted that a consistent reduction in the numbers of bacteria was found only in the material obtained in the small intestine and not in other regions of the di-gestive tract. They studied the oxygen uptake and carbon dioxide evolution of the intestinal contents in vitro, and they found that these values were low-ered in the case of chicks fed a supplement of chlortetracycline, perhaps in-dicating a decreased use of nutrients by the microflora, which might permit greater utilization of nutrients from the diet by the host animal. The mesenteric blood vessels along the small intestine were noted to be more dilated in the birds receiving the antibiotic supplemented diet.

Smyser and associates[103] found that dietary penicillin produced during si[x] weeks a steady increase in the numbers of *Clostridium perfringens* in the fec[es] of chicks. This observation seemed to rule out the possibility that the growth effect was related to a suppression of *Cl. perfringens*. Chlortetracycline pro-duced only slight changes in the count.

Another source of difficulty in carrying out investigations of the effects o[f] dietary antibiotics on intestinal bacteria is because the presence of the anti-biotic in intestinal contents may prevent the growth of the bacteria whe[n] plated out.[104]

Effect on Rumen Microorganisms

A number of investigators have made observations on the effect of anti-biotics on the rumen microflora. Loosli and co-workers[105] did not observe an[y] striking difference in the total bacterial count or in the morphologic type o[f] bacteria present based on stained slide examination in studies with Holstei[n] calves fed chlortetracycline. In experiments with beef heifers, Neumann and co-workers[106] stated that the types of organisms found in the animals receiving chlortetracycline were much less diverse than in the controls, which suggested that the normal bacterial flora had been disturbed. Kesler and Knodt[107] found that rumen samples taken from calves fed oxytetracycline showed consistently lowered ability to digest cellulose in vitro as compared with the samples from control calves. These differences disappeared when the antibiotic supplemen-

of indicator microorganisms in the rumen when chlortetracycline was fed to dairy calves. The supplemented animals were superior to the controls with respect to gains in body weight, feed intake, and efficiency of feed utilization These investigators and Kesler and Knodt reported that the antibiotic supplementation had no significant effect on the thiamine and riboflavin levels of the rumen contents although Chance and co-workers[109] found that the amount of riboflavin in the rumen contents was lower when 0.5 Gm. of chlortetracycline was fed daily than when the antibiotic-free ration was fed. In another investigation Chance and co-workers[110] reported that a definite increase occurred in the total bacterial count of the rumen contents and feces when chlortetracycline was included in the ration. The number of rumen streptococci decreased in the two fistulated animals that were used in the study Horn and co-workers,[111] in studies with yearling steers, reported that the rumen contents of animals receiving chlortetracycline showed a decreased ability to digest fiber in vitro and similar observations were made by Radisson and co-workers [112] however these investigators noted that, when alfalfa hay was added to the culture medium, no depressing effect of chlortetracycline on cellulose digestion occurred, indicating that alfalfa hay contained a factor that prevented chlortetracycline from depressing the digestion of cellulose in vitro by cultures of rumen bacteria. It is evident that studies of cellulose digestion in vitro do not necessarily reflect the behavior of the rumen bacteria in the living animal. Rusoff et al[113] did not find differences between control calves, chlortetracycline injected calves, and those fed chlortetracycline orally with respect to the rumen contents. Measurements were made of *p*H and the content of eight of the B vitamins in the rumen fluid together with an examination of the rumen flora and the degree of fiber digestion in vitro Lodge and co-workers[114] found that the digestion of cellulose in vitro by the rumen microorganisms was lower in the case of cows that had received a daily supplement of 240 mg of chlortetracycline from an early age The presence of chlortetracycline was demonstrated in the rumen liquid. These authors also noted that the addition of 1.6 μg of chlortetracycline per ml. of fermentation mixture severely inhibited cellulose digestion in vitro by the microorganisms from the control cows but had very little effect on the digestion of cellulose by the microorganisms obtained from the antibiotic-fed cows perhaps indicating the establishment of chlortetracycline-tolerant cellulolytic microorganisms in the antibiotic-fed animals.

Huhtanen and co-workers[115] have described techniques for studying the digestion of fiber in vitro by rumen microorganisms Depressions of the digestation was discontinued. Hibbs and co-workers[108] found changes in the ratings

tion of fiber were observed when antibiotics were added. However no depression of the digestion of cellulose as present in alfalfa was observed[116] to result from feeding chlortetracycline to sheep thus recalling the results reported by Radisson.[112]

Studies of the effect of chlortetracycline on the rumen microorganisms were reported by Mann and co-workers.[117] The antibiotic was fed in doses of 40 to 60 mg to young calves for several weeks following which the animals were slaughtered and the contents of their paunches and abomasums were examined. The chlortetracycline-fed calves showed no marked bacteriologic differences from the controls and the authors commented that there was little difference between the supplemented and control calves in the final development of a typical viable streptococcal population of the rumen The supplemented calves had larger and less acid rumen contents than the controls and reached a rumen *p*H that was considered to be suitable for intensive rumen bacterial and protozoan action at a much earlier age

Antibiotic tolerant Intestinal Microorganisms *as a Source of Unidentified Growth Factors*

Following the addition of an antibiotic to the diet, microorganisms that are tolerant to the presence of the antibiotic in culture media may be recovered from the intestinal contents[118] One possible explanation of the antibiotic growth effect in animals could be that these tolerant microorganisms produce vitamin like growth factors that are not present in sufficient quantities in the diet to enable maximum growth of the host animal to take place and that are not produced by the intestinal flora at a sufficient rate in the absence of antibiotics in the diet. There have been several investigations of this possibility Kratzer and co-workers[96] found that the number of yeasts increased five- to tenfold in the intestinal tract of young turkeys that received streptomycin. These yeasts were plated out and grown in large flasks following which they were harvested and fed to chicks and turkeys There was no consistent growth response and, although slight increases were found in some experiments, they were less than those obtained with antibiotic supplements

A fresh attack on this problem was made by Romoser and co-workers[119] who noted that *E. coli* and *Aerobacter aerogenes* increased in numbers in the ceca of penicillin fed chicks. These penicillin resistant organisms were isolated, grown in mass cultures under various conditions, and fed to chicks. In some experiments the cultures were lyophilized. The chicks received basal diets that were considered suitable for obtaining responses to unknown growth

factors." Little or no chick growth response was obtained when either organism was added to the diet in the absence of an antibiotic but a significant growth response was obtained to penicillin alone and a greater response to the com bination of penicillin and cultures of the organisms as dietary supplements. It was considered in view of the small amount (022 per cent) of the supplement that the results were due to effects of the viable organisms rather than to unidentified growth factors in the cultures, and the possibility was raised that the organisms aided" the antibiotic in reducing the number of inhibitory in testinal bacteria. However no experiments with heat inactivated cells were included.

Along similar lines Anderson and co-workers[91, 120, 121] isolated various strains of E. coli from penicillin fed chicks and fed the cultures to other chick ens. One strain of *E coli* produced a growth response in the presence of peni cillin but not in its absence while a second strain somewhat improved growth under both conditions. In another experiment only one out of five supplements, the culture filtrate, increased the growth rate of the chicks and then only in the presence of penicillin Similar preparations were tested with turkey poults[121] but no significant weight increases were found except that responses were obtained to penicillin itself In a further report[122] the conclusion was drawn that the growth response of chicks to antibiotics was associated with an increase in intestinal coliforms because the growth response and the increase took place simultaneously Roberts[123] has reported that the growth of chicks was increased by either *E coli* or fish solubles and Blaylock and co-workers[124] found that either of these supplements produced a growth increase of 11 per cent in chicks during the first three weeks. The control diet for such experi ments ought to be supplemented with the unfermented culture medium, for the medium may contain supplements that improve the diet. The comparatively small growth responses that are obtained with experimental animals when sources of unknown factors" such as bacterial and yeast cultures, are added to the diet present certain difficulties of interpretation Much depends on the basal diet that is used to evaluate "unknown growth factors in materials such as fish solubles, liver yeast, and distillers solubles. The diet should be complete and balanced with respect to the known growth requirements of the animal, in cluding amino acids, vitamins, and minerals. Recently Scott et al[125] and Couch and co-workers[126] have found that chicks will show a growth response to the ash of certain sources of unknown growth factors and similar results have been obtained in our laboratory There is no evidence that antibiotic-adapted forms of *E. coli* or other intestinal bacteria are better sources of nutritional factors than those bacterial forms that normally inhabit the intestinal tract.

The results with *E coli and other intestinal organisms* when fed to either antibiotic-supplemented or unsupplemented animals indicate that cultures of these organisms will not consistently produce a growth response when added to the diet. Furthermore, when feeding the culture produces a growth response in the absence of antibiotics in the diet, the response may be less than the *response to adding an antibiotic. It is* possible that antibiotic-tolerant strains *of intestinal organisms may displace harmful bacteria from the digestive tract.* The investigations just cited[125, 126] probably indicate that beneficial nutritional effects may be produced by antibiotic-tolerant intestinal organisms.

Growth of Animals Receiving Hydrolyzed Penicillin

The effect of penicillamine (β β-dimethylcysteine) on rats fed a low-choline diet was described by Wilson and duVigneaud.[127] They found that the L isomer was toxic and its injurious effects were counteracted by choline and ethanolamine. The D-isomer which is a hydrolytic product of penicillin, was not toxic. Experiments in our laboratories with chicks showed only a slight growth response to an enzymatic hydrolyzate of penicillin (table VII) The response appeared to be not more than 10 per cent of that given by the unhydrolyzed antibiotic. L-penicillamine was found to depress growth markedly when added at a level of 3 Gm./Kg. to a purified diet containing choline.

Elam and co-workers[128] reported that penicillin, inactivated by autoclaving, produced a growth response when injected into chicks but not when added to

Table VII

Effect of Procaine Penicillin and Penicillinase-Hydrolyzed Penicillin, on the Growth of Chicks

Supplement per Kg of diet Gm	Weights at 25 days, Gm.	
None	226,	229
2 mg. procaine penicillin	329	324
5 mg procaine penicillin	306,	325
5 mg hydrolyzed penicillin	277	282
10 mg hydrolyzed penicillin	278,	294

There were 10 chicks in each of duplicate groups.

Table VIII

Microbiologic and Chick Assays of Penicillin in Feed

Treatment of feed	Per cent of penicillin remaining	
	Microbiologic assays	Chick assays
Steamed 5 minutes*	43	64 46
Steamed 15 minutes	21	28 56, 50 14
Steamed 30 minutes	18	20 20 32 30
Stored 2 weeks at 34 C.	23	29
Stored 4 weeks at 34 C.	12	19
Stored 4 weeks at 34 C.†	48	67
Stored 4 weeks at 34 C.†	17	40

Dibenzylethylenediamine penicillin.
†Procaine penicillin two different samples.

the diet. An examination of their results shows that the response with the injected hydrolyzate was obtained in one experiment but not in a second experiment. Fell and Stephenson[129] reported that DL-penicillamine produced a growth response when injected but not when added to the diet however in their experiments penicillin did not produce a growth response when added to the diet. Taylor and Gordon[130] carried out 3 experiments with pigs in which penicillin inactivated by three different methods was compared with active penicillin for its growth-promoting effect on pigs. The pigs receiving penicillin grew at a rate of 14.3 per cent greater than the controls and with inactive penicillin the growth rate was 9 4 per cent more than the controls No penicillin was detected in the gut, serum, or urine of the experimental animals. Williams and co-workers[131] found that inactivated penicillin retained not more than a small part of the ability of the original antibiotic to promote the growth of chicks It was found possible to plot a dosage response curve to levels of penicillin on a purified sucrose-casein diet so that feeds containing penicillin could be assayed with chicks Chick diets containing 25 or 50 mg./Kg of penicillin were stored under various conditions or steamed and were assayed microbiologically and with chicks. The rates of inactivation of penicillin were

very similar when measured by either procedure as shown in table VIII. The chick assays gave slightly higher values but there were rather wide variations in the chick assays. The conclusion from the results in table VIII is that the hydrolyzate did not have more than a small portion of the activity of the original penicillin when tested with chicks. It is possible that hydrolyzed penicillin, even though inactive for the test organism *Micrococcus pyogenes* var *aureus*, might retain some slight activity against some of the intestinal bacteria. Recently we have compared the growth response to penicillin and D-penicillamine with chicks on the sucrose-casein diet and D-penicillamine was found to produce a growth response corresponding to about 3 per cent of that produced by procaine penicillin.

Effects of Prolonged Usage of Dietary Antibiotics

Reduction of the Antibiotic Growth Effect Following the Prolonged Use of Antibiotics in Diets When antibiotics are routinely used in the diets of animals, one can speculate that prolonged use, year after year might produce selective changes in the environmental bacteria so that antibiotic-resistant forms would gradually become more common. If some of these resistant bacteria were pathogenic or harmful, then one would expect that the antibiotic growth effect would disappear and that animals would grow at a rate corresponding to the rate seen in similar animals before the introduction of antibiotic feeding

Actually the recorded observations have been in the opposite direction and the prolonged use of antibiotics has often resulted in a gradual improvement in the growth rate of unsupplemented animals in quarters where antibiotics have been routinely used for several years. Perhaps certain growth-depressing bacterial forms tend to disappear from the environment so that the increased growth rate of animals is eventually seen in both the supplemented and unsupplemented groups. It is also possible that antibiotic-resistant bacteria may produce increased quantities of certain unidentified growth factors. The possibility of an environmental clean-up due to antibiotic feeding came to our attention in 1949 and 1950 when the response to antibiotics in chicks in our laboratory appeared to diminish over a long series of experiments, although the chicks receiving antibiotic supplements continued to reach a weight of 300 Gm. or more at 25 days.

Waibel and co-workers[123] compared the weights of chicks at 8 weeks of age with the percentage growth response of chlortetracycline or penicillin in a series of experiments lasting from August, 1950 to July 1953. The quantitative response to antibiotics tended to vary inversely with the growth of the control

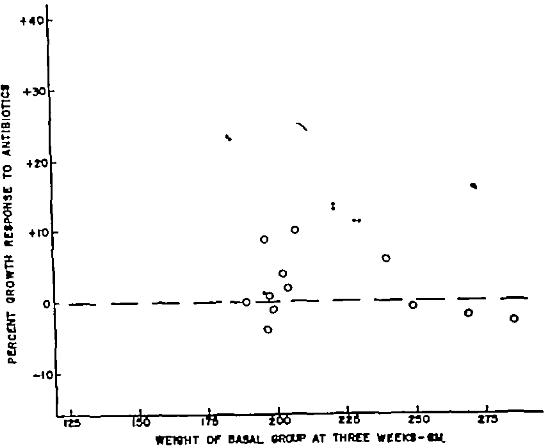


FIGURE 2

groups and the average weight of the control groups in the third year of the study was greater than during the first two years. A wide variety of diets was used. A scatter diagram of these results is in figure 2.

Libby and Schaible[133] summarized their findings with 3900 chicks in 146 comparisons between groups of birds that were fed antibiotics or arsonic acids and groups that received the unsupplemented control diets. The results are shown in table IX. A steady increase in growth rate and a decrease in mortality of the unsupplemented birds were noted. The authors pointed out that the results do not support a concept that the continued use of antibiotics in feeds can lead to the proliferation of resistant strains of organisms that can cause antibiotics to become ineffective Instead, the authors state, the continuous use of antibiotics over a long period " produces an environment with a lowered germ load or disease potential. After long time usage these growth promotants

Table IX

Growth Responses to Dietary Antibiotics and Arsonic Acids in Successive Years Compared with Control Group in Experiments with Chickens

Period	Increase in weight of supplemented birds by comparison with control birds, %		Increase in weight of control birds with respect to 1950—1951 controls, %	Mortality to 6 wks. of age %
	Antibiotics	Arsonic acids		
1950—1951	19 0 (75)†	16.0 (2)	0	8.5
1951—1952	12.8 (32)		7.4	8.2
1952—1953	10 0 (4)	3.8 (5)	15.3	4.6
1953—1954	3.3 (19)	3.2 (9)	19 1	2.8

Taken from Libby and Schaible [m]

†*Number of comparisons in parentheses.*

are still capable of suppressing the germ load, but less of a challenge is presented. Thus, birds that are grown on the premises where birds have or have had antibiotics or arsonic acids in their feeds benefit to some extent from the improvement in environment.

"The reduction in the mortality of chicks that we have observed during the last 4 yr adds support to the postulation that a reduced germ load develops. As can be seen in column 5, prior to the inclusion of antibiotics and arsenicals in chick rations, the mortality of battery-raised chicks up to 6 wk of age was about 8.5 percent, whereas the mortality of birds in these same batteries in recent years has declined to less than 3 percent. In addition, fewer cull chicks and less variability in growth rate within pens are now being noted.

"From the practical point of view this study indicates that antibiotics and arsonic acids would be of greatest value in promoting growth (i) when first used in a poultry-feeding enterprise and (ii) under the environmental conditions usually surrounding farm feeding If once used and then discontinued, feeding performance may still be somewhat improved, because the contamination level has been lowered."

Experiments with pigs have also shown that the growth of unsupplemented controls may tend to improve from year to year in surroundings where antibiotics are fed, thus Catron has found in an unpublished summary of a five

year study (1949 to 1953) involving 690 pigs that the average daily gains of antibiotic-fed pigs in successive years were 1.64, 1 60 1 60 1.67 and 1.57 lb., while the corresponding figures for unsupplemented pigs were 1 33, 1.44, 1.58, 1.57 and 1.57 lb Hanson and Ferrin[134] obtained the following results in successive years with proweaning pigs kept from weaning to 200 lb in the dry lot.

The basal diet was changed somewhat between 1951 and 1953 so that the results from one year to the next were not directly comparable however the results indicated that the general use of antibiotics for three years had controlled certain intestinal infections so well that these infections were not a problem in 1953. A similar trend is indicated in a report by Richardson[135] who used individually fed littermate pigs in four successive experments each of which lasted between 14 and 21 weeks. The average daily gain in pounds of the un supplemented controls rose from 1.38 in 1952 and 1953 to 1.61 in 1954 while the corresponding groups that received chlortetracycline gained respectively 16, 20 9 and 4 per cent more than the controls in successive experiments thus showing a decrease in the antibiotic growth response due to improvement by the unsupplemented controls. No response was obtained to oxytetracycline.

These experiments with chickens and pigs in which the antibiotic growth effect was shown to diminish in a series of experiments in the same rearing quarters while the growth of the unsupplemented controls improved are of great interest. The results indicate that the antibiotic growth effect is not due to a direct action on the animal but is due to a suppression of harmful bacteria and that the antibiotics or their effects may become "spread around the animal quarters so that the suppression may gradually extend throughout the

Table X

Results in Successive Years with Preweaning Pigs Kept from Weaning to 200 lb in the dry lot[134]

Year	Average daily gain lb			
	3 to 8 weeks		Weaning to 200 lb.	
	Without antibiotic	With antibiotic	Without antibiotic	With antibiotic
1951	0 37	0.64	1 40	1.63
1952	0 43	0.71	1 45	1.63
1953	0.63	0 73	1.74	1.79

premises. An additional possibility is that certain antibiotic-tolerant bacteria, which become established through the use of diets containing antibiotics, may have a beneficial effect on nutrition. Clearly it is time to question the soundness of the dire prediction that the prolonged feeding of antibiotics would encourage the widespread development of resistant strains of dangerous bacteria[136] in the poultry rearing industry From the practical standpoint, the effects of feeding antibiotics to growing farm animals for prolonged periods have led to unexpected benefits in the elimination of certain endemic types of undiagnosed morbidity Slinger and Pepper[137] noted that syndrome involving poor growth, high mortality dermatitis, and diarrhea in young turkeys was overcome by the use of antibiotics and, furthermore, that this syndrome, which was one of the major problems involved in rearing poults in Ontario, has largely disappeared following the inclusion of antibiotics in commercial diets.

The continuous administration of streptomycin and oxytetracycline at high levels (0.02 and 0 04 per cent) in the diet of aged rats, beginning at the age of 11 months, was not found to be beneficial as regards longevity in studies by French et al.[128] The average life span of the supplemented animals of both sexes was decreased by about 10 per cent. It was thought that, by analogy with their results on a high fat diet, an increased efficiency of food utilization might have been responsible for the deleterious effect. However an examination of the results indicates that the difference in the life span between treated and control animals did not reach significance at the 5 per cent level. No beneficial or deleterious effects of the antibiotic supplementation were shown by gross and histologic examination.

CHAPTER III Effect of Feeding Antibiotics On the Requirement for Nutrients

Improvements in the utilization of protein and of certain vitamins and minerals have been noted to be associated with the feeding of antibiotics in some experiments. These improvements are separate from the antibiotic growth effect, which has been obtained on diets that were adequately furnished with the known requirements for growth and in some cases also with additional amounts of certain vitamins and sources of "growth factors" such as liver.[5]

Antibiotics have been shown in many investigations to enhance the utilization of certain nutrients, shown by a lower requirement for the nutrient for the production of maximum growth in the presence of the antibiotic, by a greater growth response to the antibiotic at suboptimal levels of the nutrient than when an optimal level of the nutrient is supplied, by a greater growth response to a small increment of the nutrient in the presence of the antibiotic than in its absence, by increases in the tissue levels of the nutrient, or by its increased urinary excretion or deposition in the egg when the antibiotic was fed. It appears in the case of some of the vitamins that antibiotics improve their uptake from the gut or their synthesis by the intestinal bacteria, or both. It also appears that the uptake of calcium and manganese may be improved by antibiotics.

In the case of the protein requirement, the situation is more obscure: in some investigations it has appeared that the protein requirement or the requirement for a specific amino acid for maximum growth was lowered by adding antibiotics and in others no protein sparing effect was noted. These differences may reflect variations in the intestinal bacteria of the animals in the various experiments.

There is a large amount of experimental evidence that establishes an effect of antibiotics in improving the efficiency with which food is converted to an

increase in body weight in growing animals. This effect may be an indicatio of an improvement of the uptake of various nutrients from the intestinal tra and this in turn can lead to measurable effects of dietary antibiotics on th requirement for protein, vitamins, and energy depending upon the manne in which the postabsorptive utilization of the nutrients takes place.

Effects on Vitamin and Mineral Requirements

B Complex Vitamins Emerson and Smith[139] produced a biotin deficiency i rats by adding streptomycin to a purified diet. This deficiency can also be pro duced by adding sulfonamides to purified diets for rats. Streptomycin appear to differ from some of the other antibiotics in this effect. In 1948 we made a unsuccessful attempt to produce folic acid deficiency in rats on a purified die by adding a high level of chlortetracycline.

The first preparations of antibiotics that were widely used in animal feed contained chlortetracycline and vitamin B_{12} and the response that this combina tion produced in animals on "all vegetable" diets led to the wide impressio that there was some interrelation between the antibiotic and vitamin B_{12} in the growth response In some investigations it was shown that an antibiotic supple ment had a sparing effect upon the vitamin B_{12} requirements of chicks or pig but in other experiments the growth response to the antibiotic and the vitamin appeared to be independent of each other Sparing effects on other vitamins were reported by many investigators.

Common and co-workers[140] found that blood levels of riboflavin and cal cium in chicks were increased when chlortetracycline was fed, perhaps indicat ing that the absorption of these substances from the intestine was improved by the antibiotic. Biely and March[141] reported that chlortetracycline had a sparing effect on riboflavin, niacin, and folic acid in the growth of chicks Some evi dence for a sparing effect of chlortetracycline on the riboflavin requirements of chicks on purified diets was noted in our laboratory[43] Oleson and co workers[142] found a sparing effect of chlortetracycline on the vitamin B_{12} re quirements of chicks while Stokstad and Jukes[143] found that chlortetracycline reduced the vitamin B_{12} requirement of chicks in some experiments but not in others. The high mortality of young chicks associated with a deficiency of vitamin B_{12} was reduced by feeding chlortetracycline. Waibel and co-workers[144] found that penicillin or chlortetracycline markedly increased the growth of chicks fed diets containing suboptimal amounts of thiamine, but, when the level of thiamine in the diet was adequate, the growth response was only slight, thus indicating a sparing effect on the thiamine requirement. The

authors suggested that synthesis of thiamine by the intestinal flora might have been improved by the antibiotic. In another publication Waibel and co-workers[145] observed that the addition of penicillin to the diet of laying hens resulted in increased deposition of biotin and folic acid in the egg yolk.

Linkswiler et al[146] noted that rats on inadequate levels of pyridoxine showed a somewhat greater growth response to chlortetracycline than rats on adequate levels of the vitamin, thus indicating a sparing effect of the antibiotic on the requirement of vitamin B_6. These investigations were extended considerably by Lih and Baumann[147] who compared the growth-promoting effects of various antibiotics for rats on diets deficient in B vitamins. The experimental data were not conclusive because the growth-promoting effects of the antibiotics were in most cases measured only at suboptimal levels of the vitamins; however, in the case of pantothenic acid there was some evidence of a sparing action. Chlortetracycline was found by McDaniel and Daft[148] to accentuate the signs of vitamin B_6 deficiency in rats while penicillin had a beneficial effect on growth and survival and in reducing the severity of dermatitis. This is in contrast with the findings for chlortetracycline reported by Linkswiler et al.[146]

Coates and co-workers[149] studied the vitamin requirements of chicks on purified diets deficient in the various members of the vitamin B complex as influenced by the addition of pencillin to the diets. No sparing effect was found for thiamine, riboflavin, pyridoxine, or pantothenic acid but the requirements for biotin and folic acid were reduced. In the case of niacin, the requirement appeared to be increased. Nelson and Scott[150] found no effect of chlortetracycline or penicillin on the niacin requirement of chicks on a purified diet. They noted that the antibiotic growth effect disappeared when the diet was severely deficient in niacin, which was in contrast with our findings,[43] although we noted that the antibiotic growth effect disappeared or was greatly diminished when chicks were severely deficient in riboflavin, pantothenic acid, or folic acid. The food intake is extremely low under highly deficient conditions so that very little growth takes place. Sarett[151] found that the oral administration of 4 to 6 Gm. of streptomycin daily was followed by a marked decrease in the urinary excretion of biotin in human subjects. The effects on the excretion of other B vitamins were variable and not marked. The quantitative urinary excretion of certain products of tryptophane metabolism was not changed by the administration of streptomycin. In studies with rats, Halevy and co-workers[152] found that streptomycin reduced the urinary excretion of folic acid and biotin. The folic acid content of the liver and the amount of biotin in the contents of the cecum were reduced. Varying effects were produced by the other antibiotics: chlortetracycline had a slight sparing effect on niacin, folic

acid, and biotin, oxytetracycline, on niacin and folic acid, but no effects on the requirement for these vitamins were found for penicillin. In an investigation by Sauberlich[153] on the requirement of weanling rats for certain B vitamins, sparing effects on the requirement for thiamine and pantothenic acid were obtained with chlortetracycline and penicillin and the requirement for pyridoxine was spared by penicillin as judged by the fact that marked growth responses were obtained to the antibiotics on the deficient diets while their inclusion in the completely vitamin supplemented diet had no effect upon growth of the animals. In contrast, sulfamerazine depressed growth on both the supplemented and deficient purified diets. Schendel and Johnson[154] studied the effects of penicillin and chlortetracycline on rats receiving suboptimum levels of thiamine and pantothenic acid administered both orally and subcutaneously Marked increases in growth were produced by the antibiotics and the growth responses were absent when the diets were adequately supplemented with thiamine and pantothenic acid. The results were not affected by the mode of administration of the vitamins. The amount of pantothenic acid in the intestinal contents of rats on the deficient diet was increased when chlortetracycline was given Along similar lines, Chow and co-workers[155] found that the oral administration of any of several antibiotics increased the apparent formation of vitamin B_{12} by the intestinal bacteria as indicated by a rise in the butanol-soluble radioactive fraction following the administration of cobalt[60]

The effects of antibiotics on the requirement of animals for vitamin B_{12} have been studied with varying results. Several reports have shown definite improvements produced by feeding antibiotics on the hatchability of hens eggs or on growth of rats, chicks, or pigs when the animals were fed B_{12} deficient diets while in other investigations no changes were produced.

Johansson and co-workers[87, 156] found that growth responses were produced in rats by adding chlortetracycline and vitamin B_{12} singly or in combination to a diet deficient in vitamin B_{12} The responses appeared to be independent of each other and no increase in the apparent vitamin B_{12} content of the kidney and liver tissue was produced by feeding chlortetracycline, but increases were found, not unexpectedly when 25 µg/Kg. of diet of B_{12} were added. Of interest was the observation that chlortetracycline produced increases in the vitamin B_{12} activity as determined with *E coli* 113-3 in the supernatant liquid obtained by suspending the contents of the colon and cecum in water and centrifuging off the solids. However *E coli* 113-3, responds to cobalt-containing B_{12}-like substances that will not alleviate vitamin B_{12} deficiency in animals

Cravioto-Munoz et al[157] found that chlortetracycline produced a marked growth response in rats on a B_{12}-deficient, purified diet to an extent that led

these authors to state that chlortetracycline could replace vitamin B_{12} in the diet of the rat. Autoclaved chlortetracycline was ineffective No unsupplemented group was included.

The effect of antibiotics on the vitamin B_{12} requirements of pigs has varied in different experiments. For example Catron and co-workers[54] found that chlortetracycline and vitamin B_{12} both increased the growth rate of pigs on a corn-soybean diet and that the growth response to the vitamin was the same in the presence or absence of the antibiotic, while in another investigation[105] vitamin B_{12} produced a 14 per cent growth increase in the absence of chlortetracycline and no increase in its presence. Sheffy and co-workers,[189] in a study with baby pigs on a semisynthetic milk, recorded the following daily gains no supplement, 0.26 lb vitamin B_{12} 0.36 lb chlortetracycline 0 40 lb B_{12} plus chlortetracycline, 0 47 lb These results indicated a sparing effect of chlortetracycline on the vitamin B_{12} requirement. On the other hand, baby pigs that were highly deficient in vitamin B_{12} did not show a growth response to chlortetracycline in a study by Wahlstrom and Johnson.[196] Monson et al[10] made an interesting study with chicks that received diets containing insufficient amounts of folic acid, which were supplemented with antibiotics They found that coliform organisms, which produced increased amounts of cellular folic acid in vitro appeared in the duodenum and ileum following the administration of antibiotics. Simultaneously the folic acid content of the liver of the chicks was increased. This may be a further indication that antibiotic-resistant intestinal bacteria are in part responsible for the beneficial nutritional effects of dietary antibiotics.

It is evident from various investigations already described, which may be taken as representative of the large volume of work in this field, that dietary antibiotics in many cases improve the nutrition of animals with respect to the B vitamins, but in other cases the antibiotics are without any effect on the B vitamin requirement. A few exceptions have been noted, especially the case of streptomycin which appears to reduce the synthesis of biotin in the intestine. Antibiotics improve the production of B vitamins by the intestinal bacteria or the absorption of B vitamins into the blood stream.

Some effects of dietary antibiotics in modifying the requirements for animals for B complex vitamins were expected in view of the well known relationship of the intestinal and rumen microflora to synthesis of these vitamins. There was less basis for expecting an effect on the utilization of minerals and fat soluble vitamins However experimental work soon uncovered such relationships

Vitamin A and Carotene Burgess and co-workers[29] found that dietary

penicillin improved the utilization of vitamin A and carotene in chicks. Significant increases were found in the vitamin A content per Gm. of liver and in the blood level of carotenoids when penicillin was fed and the chicks were compared with control birds at 26 days of age. Along similar lines, Coates and co-workers[30] noted that the liver storage of vitamin A was improved by feeding penicillin to chicks and that the conversion of β-carotene to vitamin A in the intestinal wall was increased. The same effects were produced by placing the chicks in isolation units, which prevented contact with "infections Further investigations in this field were made by Almquist and Maurer[20] who employed a diet containing only vegetable sources of vitamin A activity in contrast to the diet used by Burgess and co-workers, which contained both carotenoids and fish oil sources of vitamin A activity The findings are shown in table XI, liver vitamin A was increased slightly by the lowest level of antibiotic fed and

Table XI

Vitamin A and Carotene in Chick Livers as Related to Feeding of antibiotics[20]

Supplement per Kg of diet	Liver vitamin A (I U/Gm.)		Liver carotene (µg./Gm.)		Average body wt Gm.	
	8 wk.	10 wk.	8 wk.	10 wk.	8 wk.	10 wk.
None	45	83	2.6	5.6	980	1363
4.5 mg antibiotic mixture†	55	94	3 1	7.6	989	1389
55 mg chlortetracycline	—	115	—	8.8	1070	1387
110 mg chlortetracycline	113	115	4.8	7.2	1076	1446

*Practical diet containing only plant sources of vitamin A activity approximately 11 I U/Gm.

†Chlortetracycline plus penicillin.

higher levels led to further elevations in both liver vitamin A and carotene. It was concluded that maintenance of a healthier intestinal condition in the presence of an antibiotic was responsible for improved conversion or absorption of carotene or both. It is of interest to compare the effect of antibiotics in preventing liver necrosis,[45] an effect that is also produced by vitamin E, with their effect on vitamin A metabolism. Vitamin E has been reported in some

investigations to improve the utilization of vitamin A, possibly by protecting it against oxidation.

No sparing effect of chlortetracycline on vitamin A was found in experiments with rats by Hartsook et al[161] and chlortetracycline appeared to enhance the vitamin A deficiency syndrome when added to a diet free from the vitamin, as judged by earlier appearance of the signs of the deficiency and a shorter time of survival.

In contrast Murray and Campbell[162] found that the addition of chlortetracycline to a vitamin A free diet for rats increased their response to graded doses of vitamin A acetate. The mean increase of many tests was 24 per cent. The effect was also observed when chlortetracycline supplementation was begun 24 hours after the last dose of vitamin A, which made it appear that the improved utilization was not due to an increase in absorption of vitamin A from the intestine. The time required for depletion of the liver stores of vitamin A was lengthened by dietary chlortetracycline.

The storage of vitamin A in the livers of pigs fed various supplements was measured by Barber and co-workers.[163] They found that on the basal diet the livers contained 12.8 units/Gm. of vitamin A, with chlortetracycline added, 19.3 and 19.6 units/Gm. with penicillin, 13.1 units/Gm. and with a mixture of penicillin and streptomycin residue 13.2 units/Gm. Chlortetracycline but not penicillin increased the liver storage of vitamin A.

Penicillin was found to produce increases in the vitamin A content of the liver of chicks on a normal diet and to increase the levels of carotenoids, ascorbic acid, and phospholipid phosphorus in their blood plasma.[164]

High[165] found that chlortetracycline, 50 mg/Kg. of diet, increased the deposition of vitamin A from carotene in the liver and kidneys. Rats receiving 80 μg. carotene as the sole source of vitamin A deposited 50 μg. of vitamin A in the liver and kidneys while chlortetracycline-fed rats deposited 63 μg. The storage of preformed vitamin A was not affected by the antibiotic. Penicillin had no effect on storage of vitamin A from carotene-fed rats. These results are similar to those reported by Barber and co-workers with pigs[163] in that chlortetracycline but not penicillin increased liver vitamin A storage on a diet containing carotene. The results with chicks differ for both Coates and Burgess reported increases in the liver vitamin A of chicks following the addition of penicillin to a diet containing carotene.

Vitamin D Calcium and Phosphorus Investigations by Ross and Yacowitz[166] indicated that penicillin appeared to decrease the vitamin D requirement for normal bone calcification. An increase in bone ash of chicks at three weeks was observed to be produced by adding penicillin to a diet containing

penicillin improved the utilization of vitamin A and carotene in chicks. Significant increases were found in the vitamin A content per Gm. of liver and in the blood level of carotenoids when penicillin was fed and the chicks were compared with control birds at 28 days of age. Along similar lines, Coates and co-workers[30] noted that the liver storage of vitamin A was improved by feeding penicillin to chicks and that the conversion of β-carotene to vitamin A in the intestinal wall was increased. The same effects were produced by placing the chicks in isolation units, which prevented contact with infections." Further investigations in this field were made by Almquist and Maurer[29] who employed a diet containing only vegetable sources of vitamin A activity in contrast to the diet used by Burgess and co-workers, which contained both carotenoids and fish oil sources of vitamin A activity The findings are shown in table XI liver vitamin A was increased slightly by the lowest level of antibiotic fed and

Table XI

Vitamin A and Carotene in Chick Livers as Related to Feeding of antibiotics[29]

Supplement per Kg of diet	Liver vitamin A (I. U./Gm.)		Liver carotene (µg./Gm.)		Average body wt., Gm.	
	8 wk.	10 wk.	8 wk.	10 wk.	8 wk.	10 wk.
None	45	83	2.6	5.6	980	1363
4.5 mg antibiotic mixture†	55	94	3.1	7 6	989	1389
55 mg. chlortetracycline	—	115	—	8.8	1070	1387
110 mg chlortetracycline	113	115	4.8	7.2	1076	1446

*Practical diet containing only plant sources of vitamin A activity approximately 11 I U/Gm.
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Vitamin D Calcium and Phosphorus Investigations by Ross and Yacowitz[166] indicated that penicillin appeared to decrease the vitamin D requirement for normal bone calcification. An increase in bone ash of chicks at three weeks was observed to be produced by adding penicillin to a diet containing

suboptimal levels of vitamin D These results may be compared with earlier observations by Migicovsky and co-workers[167] who found that penicillin increased the uptake of calcium[45] when fed to chicks on a low calcium diet. Gabuten and Shaffner[168] found that dietary penicillin increased the breaking strength of eggs and the blood calcium level in hens and Bogdonoff and Shaffner[169] reported that chlortetracycline, oxytetracycline penicillin, and bacitracin increased the plasma calcium level of male chicks when added to a diet containing 2.6 per cent calcium. Penicillin was also fed with lower levels of calcium and was found to increase the plasma calcium level.

Lindblad and co-workers[170] found that the growth response of chicks and turkey poults to chlortetracycline was greater on higher than on lower levels of calcium and phosphorus.

Manganese Metabolism. Manganese is needed for growth and the prevention of a bone deformity termed "perosis in chicks and poults. An effect of chlortetracycline on the utilization of manganese was described by Pepper and co-workers.[171] They found that the amount of manganese requirement to prevent perosis in chicks was lowered by adding chlortetracycline at a level of 10 mg /Kg of diet.

Effect on Protein Requirement

A large number of experiments have been carried out to investigate the effect of dietary antibiotics on the level of protein required by poultry and swine for maximum growth. The economic importance of this question is obvious, for the supply of proteins of high biologic value may limit the numbers of poultry and pigs that can be produced on a nationwide basis. In some ex periments it was found possible to produce maximum growth with slightly lower levels of protein in the presence of dietary antibiotics than in their absence. Other investigations have indicated that no difference in the protein requirement was produced by feeding antibiotics.

The protein requirement for maximum growth of chicks was found by Machlin and co-workers[172] to be 19 per cent with a diet containing chlortetra cycline and 21 per cent if the antibiotic was omitted. Weakley and coworkers[173] concluded that bacitracin, chlortetracycline, and penicillin all had a sparing effect on the protein requirement of chicks. Chlortetracycline and penicillin were found to improve the growth of chickens at four different levels of protein, and there was evidence that the utili of both protein and energy was improved by the antibiotics, but indica the

protein level for maximum growth was lowered.[174] Scott and co-workers[175] concluded that in their experiments the protein requirement of chicks was not changed by adding 15 mg. of chlortetracycline per Kg of diet. Growth and nitrogen retention were measured in chicks on various levels of protein with and without penicillin by Saxena and co-workers.[176] The increase in weight that accompanied penicillin feeding was the same at all levels small but not significant increases in nitrogen retention were found in the birds receiving the penicillin supplement at the lowest level of protein (15 per cent) Turkeys showed an improved response to penicillin as the level of fishmeal in the diet was increased,[177] and the greatest feed efficiency was obtained with penicillin and the highest level of fishmeal. Slinger and co-workers[178] deduced that the requirement for lysine was increased, simultaneously with the growth rate, by adding antibiotics to a diet containing 20 per cent protein. The lysine deficiency which manifests itself in young turkeys by the appearance of white feathers was not seen when the antibiotic-supplemented diet contained 28 per cent protein. Biely et al[179] found that chlortetracycline and penicillin did not affect the protein requirement of chicks or their requirement for lysine or tryptophane but did reduce the mortality on the tryptophane-deficient diet. Matterson and co-workers[180] found that chicks fed a ration containing chlortetracycline required at least 21 per cent of protein for best results as measured by growth and feed efficiency There was no indication that the antibiotic reduced the protein requirement. White-Stevens and Zeibel[181] approached the problem from the standpoint of the levels of both protein and antibiotic. Their results with chicks showed that 10 parts per million of chlortetracycline was more effective as judged by growth on the low than on the high protein diet, while higher levels of chlortetracycline were most effective at the higher protein levels, the optimum being 22 per cent protein with 100 parts per million of chlortetracycline.

Studies with pigs have led to results very similar to those reported for chicks. There is some evidence for a slight lowering of the protein requirements for maximum growth, but in many experiments the antibiotic growth effect has been observed at varying protein levels without evidence of interaction. It has also been noted that feeding an antibiotic may improve nitrogen retention.

It is customary in feeding pigs to reduce the protein content of their diets stepwise during the growing period and this practice complicates an evaluation of the effect of antibiotic supplementation on protein requirement. Catron and co-workers[182] investigated the effects of chlortetracycline on the growth of pigs receiving various levels of protein from weaning to 200 lb The results are summarized in table XII Each protein level was reduced by a step of 3

Table XII

Relation of Chlortetracycline 10 mg /lb. of Diet on Average Daily Gain and Food Utilization in Growing Pigs*

Protein levels	Chlortetracycline in diet	Average daily wt gain, lb. Initial†–75	75–150	150–200	Initial–200 Av daily gain	Feed per 100 lb of gain
20 to 17 to 14	–	1.21	1.53	1.81	1.51	390
	+	1.31	1.79	1.94	1.68	354
18 to 15 to 12	–	1.29	1.58	1.81	1.56	383
	+	1.28	1.73	2.03	1.66	360
16 to 13 to 10	–	1.26	1.67	2.02	1.63	372
	+	1.34	1.83	1.80	1.67	355
14 to 11 to 8	–	1.23	1.64	1.54	1.50	374
	+	1.26	1.84	1.88	1.66	359

*The protein levels of the diets were lowered when the pigs reached a weight of 75 lb and again when the weights reached 150 lb [182]

†Sixteen pigs per group Initial weight 29 9 to 37.5 lb

per cent when the pigs reached 75 lb and again at 150 lb In the absence of chlortetracycline, the rate of gain for the entire feeding period varied significantly among the several groups of protein levels, and the results indicated that in the presence of the antibiotic the protein requirement was lowered so that the pigs receiving successive levels of 14, 11, and 8 per cent of protein in the presence of the antibiotic gained as well as those receiving higher levels of protein in the absence of the antibiotic. The experiments were carried out with Duroc pigs on a diet consisting predominantly of corn and soybean meal. Jensen and associates[183] fed protein levels of 10 12, 14, 16, 18, and 20 per cent, with and without 5 mg of chlortetracycline or oxytetracycline per lb. of diet, to pigs weighing 31 to 36 lb. until the pigs reached a weight of 200 lb. The

Table XIII

Increased Growth Rate in Rats Fed Chlortetracycline with Soybean Diets

Supplement/100 Gm. diet	Average daily gain (Gm.)			
	Raw soybean meal		Heated soybean meal	
	Males	Females	Males	Females
None	0.42	0.78	2.36	1.85
Chlortetracycline 20 mg	1.50	1.29	2.60	2.33
DL-methionine 0.5 Gm.	2.33	1 97	3.36	2.58
Chlortetracycline plus methionine	3.02	2.01	4.02	2.40

average daily gains of the pigs appeared to reach a maximum at between 16 and 18 per cent protein without antibiotics and at 14 per cent protein with antibiotics, but the effect was not statistically significant.

Effects on Nitrogen Metabolism

Streptomycin was found to have no effect on the utilization of food protein in rats by Black and Bratzler [184] An all-vegetable diet supplemented with vitamin B_{12} was used. In another study[185] a supplement of antibiotics was used at a lower level, 10 per cent, of dietary protein, and again no effect was found on the nitrogen retention of paired fed rats due to the supplement. The utilization of energy was improved by the antibiotics.

Carroll and co-workers[186, 187] investigated the effects of chlortetracycline and methionine on the utilization of nitrogen in diets containing either raw or heated soybeans when fed to rats. The amount of nitrogen absorbed from the diet during passage through the small intestine was increased by chlortetracycline but not by methionine The antibiotic also improved the absorption of lysine leucine, methionine and cystine. A marked increase in growth rate accompanied the feeding of chlortetracycline as shown in table XIII.[187] The lower availability of methionine in raw as compared with heated soybeans is well established. The authors concluded that a sparing action of chlortetracycline for dietary methionine was suggested by these results, either due to an

CHAPTER IV Antibiotics in Animal Production

The theoretical and experimental examinations of the mode of action of antibiotics give way to practical considerations when the effect of these substances in the diet is measured in terms of animal production, and it is in this field that antibiotics have made one of their greatest contributions The steady increase of the human population makes it incumbent on chemical technology to furnish means of increasing the supply of food. The use of antibiotics has increased the supply of meat by lowering the death losses of young farm animals and by improving the efficiency of conversion of feed into meat. Lassiter[196] stated that the feeding of antibiotics to farm animals has brought about a new era in livestock production. The following appraisal of the effects of antibiotics on swine production is summarized from an article by Catron.[197] The practical effective feeding level of suitable antibiotics for swine is approximately 5 mg./lb of feed and therapeutic levels commonly used in treating disease are 30 to 100 times as high. Antibiotics are effective in either dry lot or pasture feeding Their use increases growth rate by 10 to 20 per cent from weaning to 200 lb under average feed lot conditions with an increase in feed consumption of 5 to 10 per cent and a saving of about 5 per cent of feed required per unit of gain in growing and fattening pigs Antibiotics produce the maximum growth response when fed to young pigs and the increase in gains in pigs weighing from 100 to 200 lb is less When antibiotic feeding is discontinued after pigs reach 75 to 125 lb cessation of accelerated growth rate occurs and the growth rate tends to follow that of the control animals however the pigs previously fed antibiotics maintain their early growth advantage The number of runts is reduced and the uniformity of pigs receiving antibiotics is several times greater than that of unsupplemented controls. The response to antibiotic feeding appears to be in proportion to the disease level the practice controls a high percentage of nonspecific enteritis (scours) in swine but com-

Table XV

Effect of Chlortetracycline in the Presence of Chronic Respiratory Disease in Chicks

Pleuropneumonia-like *inoculum applied*	Av wt., Gm., at 4 wk. when chlortetracycline added, Gm./ton		
	0	50	100
None (control)	327	349	338
Inoculum applied	283	324	348

The reduction was evident in the weights at 4 weeks except on the higher level of chlortetracycline (table XV)

In an experiment under commercial conditions where chronic respiratory disease was endemic in which 5000 birds were used in each to two groups, the results at 10 weeks are shown in table XVI.

Various treatments as shown below were used in a flock of chickens in which signs of chronic respiratory disease appeared at the age of 6 weeks while the birds were on a diet containing 4 Gm./ton of procaine penicillin. The flock was divided into five groups each with about 4000 birds (table XVII).

The results are of great interest in that the efficiency of feed conversion was much lower in group 1 (unsupplemented) than in group 4 which grew at the

Table XVI

Effect of Feeding Antibiotics on Chicks with Chronic Respiratory Disease

Supplement/ton of diet	Per cent mortality	Av wt., Kg.	Gm. feed/ Gm. gain
4 Gm. procaine penicillin	10 68	1.30	3.11
4 Gm. procaine penicillin plus 100 Gm. chlortetracycline	2.82	1.40	2.81

There were 5000 chicks used in each group.

Table XVII

Results with Various Levels of Chlortetracycline on Chicks with Chronic Respiratory Disease

Gm. of chlortetracycline added/ton of diet: 6 to 8 wk.	8 to 12 wk.	Av final wt., Kg	Mortality %	Gm feed/ Gm gain
None	None	1.49	10 9	4.75
400	100	1.63	6.1	2.90
200	200	1.57	5 1	3.57
100	100	1 47	5.7	3.69
70 mg /liter in drinking water	None	1.56	7.8	3.86

same rate, indicating that the effect of the antibiotic was to improve the utilization of nutrients, rather than to increase the appetite In other experiments, the food intake per unit of body weight per day was about 20 per cent lower in groups receiving high levels of chlortetracycline than in controls. The findings by White-Stevens and his collaborators indicate the effect of a subacute disease in depressing the rate of growth and the utilization of nutrients by chicks and the action of chlortetracycline in reversing these nutritional sequelae of the disease.

Antibiotics in Swine Production

Pigs under farm conditions have been shown to be outstanding among domestic animals in growing more rapidly and efficiently when small amounts of antibiotics, especially chlortetracycline, are added to the diet. A comparison of various antibiotics, summarizing work published in 1950 to 1953 was made by Braude and co-workers[225] and table XVIII, which has been published elsewhere,[41] was condensed from their review It may be seen from table XVIII that chlortetracycline, oxytetracycline, penicillin, and streptomycin have given the best results in promoting the growth of swine Erythromycin was reported to produce no response [226]

Table XVIII

Growth and Efficiency of Feed Utilization of Pigs Receiving Various Antibiotics[225]

Antibiotic	Growth index (unsupplemented = 100)		Feed required *per unit of gain* (unsupplemented = 100)	
Chlortetracycline	135.9	(187)*	90.2	(146)
Penicillin	110.6	(53)	94.3	(44)
Streptomycin	115.2	(50)	94.4	(41)
Oxytetracycline	123.7	(23)	93.9	(17)
Bacitracin	109.0	(12)	103.0	(10)
Chloramphenicol	105.5	(6)	98.2	(6)
Neomycin	93.3	(4)	87.6	(3)
Polymyxin	96	(1)	100	(1)
Subtilin	89	(1)	130	(1)

*Figures in parentheses indicate number of comparisons.

Dried whole cultures and fermentation residues containing chlortetracycline and vitamin B_{12} were supplied by our laboratory early in 1949 to investigators who were engaged in studying the nutrition of swine. Marked growth responses, associated with the prevention of diarrhea, were soon observed and were communicated to us in the summer of 1949 by Catron, Cunha, and Krider The effectiveness of the chlortetracycline fermentation residue was contrasted with the lack of activity of a vitamin B_{12} concentrate from the streptomycin fermentation in a publication by Cunha and co-workers.[46] Further publications appeared in 1950.[26, 27, 48, 49, 227] The effects of the supplement in abolishing scouring, and in producing its most marked effects where bloody diarrhea was rampant, promptly led to the establishment of the disease level concept as an interpretation of the antibiotic growth response in pigs. This concept has been reinforced by the observation that the response in pigs has progressively diminished in many laboratories where antibiotics are fed, while the growth of unsupplemented pigs has improved and the incidence of diarrhea has lessened.

Many of the diets used in the experiments with pigs were deficient in vitamin B_{12} and consisted predominantly of corn and soybean meal so that the growth responses obtained to the crude chlortetracycline fermentation materials was due to both vitamin B_{12} and the antibiotic. Experiments with crystalline antibiotics and vitamin B_{12} soon established that both supplements were needed for optimum growth of pigs.[50]

The use of antibiotics in diets for baby pigs, such as creep feeds and artificial milks, was found to be especially beneficial in preventing mortality and producing rapid early growth. Carpenter[228] found that baby pigs receiving a creep feed containing chlortetracycline grew 43 per cent more rapidly than controls and Wahlstrom and co-workers[229] found that chlortetracycline increased the growth of baby pigs on a purified diet by 31 per cent. No effect was obtained with penicillin. Similar results were found by Noland and co-workers[94] and by Williams and co-workers.[230]

Runtness or unthriftiness in young pigs may often be successfully treated or prevented by adding antibiotics to the diet.[231-234] In one investigation[234] unthrifty pigs that were fed a diet containing 11 mg /Kg. of chlortetracycline gained three times as much weight in a five week period as did the unsupplemented controls.

The effect of the type of protein concentrate on modifying the growth response to antibiotics in pigs has been studied by several investigators. In the first published investigations with pigs, Burnside and co-workers[235] found that the crude fermentation containing chlortetracycline and vitamin B_{12} produced a markedly greater response in pigs when peanut meal was used as compared with either soybean meal or fishmeal. Barber and co-workers[162] found that the response to antibiotics was much less on a diet containing fishmeal than on an all vegetable diet and similar findings were described by Robinson et al.[236] These findings may be related to sparing effects of the antibiotics on the requirement for amino acids. Becker and co-workers[237] found in contrast to the work by Barber and Robinson that the growth response of pigs to chlortetracycline or to a mixture of antibiotics was greater with menhaden fishmeal than with soybean meal as the supplementary protein. In the absence of antibiotic, the pigs showed a growth response to tryptophane when added to the corn-fishmeal diet thus raising the question of a possible sparing effect of the antibiotic supplement. In other investigations, the response to antibiotics varied with different sources of protein but no consistent trend can be perceived and no doubt the results depend to some extent on variations in the nutritional quality of the various samples of meal that were used.[238-242]

The effect of implanting pellets of antibiotics on the growth of pigs was

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lambs appeared in 1951 when Jordan and Bell[375] found that chlortetracycline promoted the growth of lambs and decreased enterotoxemia.

Many investigators of antibiotics in the feeding of ruminants, conducted for the most part with chlortetracycline, were published in the years between 1951 and 1955. Reviews have been written by Knodt[376] and Lassiter[144] Chlortetracycline has been reported to increase the growth rate, feed consumption, and efficiency of feed utilization of young calves and lambs and to reduce the incidence of certain diseases including scours, pneumonia, and liver abscesses in calves, and enterotoxemia in lambs. With older ruminants, digestive upsets have sometimes been encountered, but it is often possible to forestall these by regulating the composition of the ration and the dosage of the antibiotic. The most marked effects have been found with unthrifty animals. Chlortetracycline and other antibiotics have been found to depress the digestion of cellulose in vitro by mixed cultures of rumen microorganisms, but such effects do not seem to be evident in the intact animal.

Effects on Dairy Calves Marked increases in the rate of growth of dairy calves during the first 5 or 6 months of life have been observed by various investigators when chlortetracycline was added to the ration. The most marked effects were observed in calves which were housed in contaminated quarters where the incidence of scours was high[377] but responses were also obtained by Bartley and co-workers[378] when the unsupplemented animals were gaining at a normal rate. Two levels of chlortetracycline were compared, 15 mg. and 45 mg /day and the higher level was found more effective in promoting growth and in reducing the incidence of various types of infections. In further studies,[379] levels of 45 and 90 mg of chlortetracycline were compared and were found to be equally effective in reducing the incidence of infections. Much larger doses, 200 to 800 mg of chlortetracycline per 100 lb of calf weight, were fed to calves without producing anorexia or weight loss or any other visible detrimental effects and one calf not previously supplemented, was given 2.5 Gm. of chlortetracycline daily between 16 and 20 weeks of age without deleterious effects Many investigations with chlortetracycline in the diets of dairy calves have been carried out by Rusoff and co-workers.[68, 115, 65, 290, 294] The antibiotic was found to increase the rate of gain of both Jersey and Holstein calves by 20 per cent over that of the control animals through 16 weeks of age. Comparisons were made between oral supplementation and intramuscular injection and the injected animals were found to grow more rapidly than those receiving the antibiotic orally These observations led the authors to conclude that the mode of action of chlortetracycline in producing the antibiotic growth response was not due to an effect in the rumen because

the injected antibiotic was shown to be present in the bile and not in the rumen contents. At autopsy the animals receiving chlortetracycline showed larger skeletal size and more meat than did the controls This was thought to indicate that the antibiotic was producing an effect on the pituitary gland. The authors were unable to detect any chlortetracycline in the pituitary spleen thymus, and muscular tissues so that it is difficult to implicate the pituitary gland on the basis of these studies No effects on the yield and composition of the milk were produced by feeding supplements of 130 mg of chlortetra cycline daily to dairy cows[284] nor were physiologic effects produced when chlortetracycline was fed to bulls at a rate of 300 mg daily[283] A decrease in thickness of duodenal and jejunal sections of the intestinal wall and an in crease in the ileal section were found in calves receiving chlortetracycline.[285]

Richardson and co-workers[286] found no growth-promoting effect of chlor tetracycline when given by intramuscular injection to dairy calves. The gains in 4 weeks were 8.2 lb for unsupplemented calves, 12.0 lb for calves receiving two levels of oral chlortetracycline, 9 0 lb for calves implanted subcutaneously with chlortetracycline, and 8.2 lb for calves injected intramuscularly with chlortetracycline.

It was noted by Roy and co-workers[287] that the beneficial effect of colostrum on calves appeared to be related to the prevention of scouring. Accordingly the effects of chlortetracycline and colostrum were compared in experiments in which 40 calves were used, and it was found that the calves receiving chlortetracycline without colostrum were protected against scours in a man ner that resembled the effect of colostrum when fed without chlortetracycline The authors made the interesting suggestion that colostrum might be impor tant for its antibacterial effect. The feeding of chlortetracycline to colostrum-deprived calves increased live-weight gain significantly and reduced the inci dence of scouring and the occurrence of abnormally high rectal temperatures. Colostrum fed calves behaved similarly to the chlortetracycline-fed calves when compared with unsupplemented controls.

No effect on milk production and feed consumption was found when chlor tetracycline was fed to mature lactating dairy cows which received 130 mg daily for 30 days,[284] 300 to 500 mg daily[288] or 700 mg. daily for 10 days.[290] The antibiotic was not detected in the milk in the latter investigation.

Antibiotics in Beef Cattle Feeding

The addition of chlortetracycline or penicillin at high levels ranging up to 600 mg daily to the rations of beef cattle was found in earlier investigations

to be followed by various effects including a loss of appetite, a depressio the apparent digestibility of crude fiber and a decrease in nitrogen re tion.[111, 291, 292] Such apparent digestive disturbances were noted to disap when the feeding period was prolonged.[104] In later investigations it was fo that chlortetracycline was tolerated better when fed at lower levels and w the diet was high in roughage, thus Tovrea[293] found the following average d gains in an experiment lasting 90 days with 20 beef cattle per group in wh the initial weight of the animals was about 660 lbs. when chlortetracycline given in doses of 0, 72, 90 and 108 mg per animal per day the average d gain was 2.76 3.12, 3.11, 3.00 lb., respectively In a second experiment, an supplemented group gained 2.61 lb. daily per head, a group receiving 80 of oxytetracycline daily 2.65 lb and a group receiving 80 mg. of chlorte cycline daily 2.81 lb.

Matsushima and co-workers[294] found that calves which were fed 15 mg chlortetracycline daily grew more rapidly than control calves and were f from scouring which occurred frequently in the controls. The calves w slaughtered at 7.5 to 10 months and 90 per cent of the supplemented cal had normal livers as compared with 10 per cent of the controls, 70 per c of which had abscessed livers, presumably from infections which ente through the portal circulation. Perry and co-workers[295] observed a mark decrease in the incidence of scours when chlortetracycline was fed at mg /100 lb of body weight daily to beef calves. The daily gain was 1.78 in the supplemented group as compared with 1.59 lb for the controls dur the 80 day experimental period. In the same investigation, the effect of chl tetracycline on older beef animals was examined. The addition of chlortet cycline to a concentrate-type of ration for yearling heifers and steers, starti at 9.1 mg /lb of grain and increasing stepwise to 27.2 mg resulted in da gains of 1.64 lb as compared to 1.52 for controls. In other experiments, mark improvements in rate of growth and cellulose digestion were observed wh chlortetracycline was added to high roughage rations (table XX) containi supplement A, which consists of 65.1 per cent soybean meal, 14 per ce molasses, 14 per cent alfalfa meal, 5.2 per cent bonemeal, 1.7 per cent with cobalt, and a concentrate supplying 2270 units of vitamin A and 2 units of vitamin D per pound of supplement.

Duitsman and Kessler[296, 297] compared bacitracin and chlortetracycline f 122 day periods in two experiments, each of which involved 10 animals p group fed 122 days on a ration of silage, milo and cottonseed meal with t result that in the first experiment those animals fed no supplement had average daily gain of 1.54 those with 45 mg daily of bacitracin added, 1.6

those with 45 mg daily of chlortetracycline added, 1 72. In the second experiment the average daily gains were 1.45 for those fed no antibiotic supplement· 1 34 for those fed 45 mg daily of bacitracin, and 1.52 when 45 mg daily of chlortetracycline was added.

The experimental work with beef cattle in which favorable results were reported was carried out principally with chlortetracycline A level of about 10 mg /100 lb of body weight was suitable and the best responses were on rations high in roughage. Setbacks may occur when antibiotics are given at high levels, especially to animals that are receiving high-concentrate diets.

Antibiotics in Lamb Feeds

The oral administration of fairly high doses of antibiotics to lambs was found to produce digestive disturbances by Colby and co-workers,[289] who noted that lambs receiving daily 100 mg of chlortetracycline or penicillin lost weight and developed diarrhea while Turner and Hodgets[298] noted that a single dose of 750 mg. of chlortetracycline to Merino sheep was followed by loss of appetite and weight. Lower supplementary levels are better tolerated. Jordan[296] and Jordan and Bell[275] found that lambs on fattening rations tolerated low dosage with chlortetracycline and there was some reduction of enterotoxemia. In further experiments,[300] chlortetracycline was fed to lambs at levels of 4.3 to 10.8 mg. daily and slight improvements in growth were seen in three of four trials. In another report, lambs receiving chlortetracycline in a pelleted ration required 10 per cent less feed per unit of gain than controls.[301] Hatfield and Garrigus[302, 303] studied the effects of chlortetracycline when 10 mg /lb was added to a concentrated feed which was offered free choice with alfalfa hay The supplemented lambs grew about 10 per cent faster than the controls and produced slightly better carcasses.

These investigators[303] summarized the results of three experiments involving 190 lambs. Rations supplemented with chlortetracycline at levels of 5.5 to 7 6 mg /lb gave small but consistently higher average daily gain and produced daily gains which were .055 ± 014 lb higher than those of the controls. The feed efficiencies and carcass grades of the supplemented lambs were higher than those of the controls. The average performance of lambs receiving diets containing oxytetracycline and penicillin was approximately the same or slightly better than that of controls but the differences were not significant. Chlortetracycline did not eliminate enterotoxemia but the authors concluded that "the improvement in gain and efficiency was sufficient to show that chlortetracycline has a practical place in lamb rations."

Bridges et al[304] fed chlortetracycline to lambs at levels of 1.1 to 15 mg./lb. of diet. Increases in the rate of gain resulting from feeding the antibiotic were small and were not statistically significant. Slight improvements in efficiency of feed utilization and in carcass grade and dressing percentage were noted in the antibiotic-fed lambs Effects of the composition of the ration on the response to chlortetracycline were recorded by Elliott and Ellsworth[307] who found an effect of the antibiotic on growth with 80 per cent of roughage and 20 per cent of grain but not with higher levels of grain while no relation between roughage level and response was found by Botkins and Paules[308] who reported that the average daily gain was 0.287 lb for the controls and 0.304 for the lambs receiving 10 mg. of chlortetracycline per lb of ration. In an earlier investigation, Botkins and Paules[309] found no response to chlortetra-

Table XX

Effect of Chlortetracycline on Growth of Beef Cattle Receiving various rations[295]

Days of experiment	No. animals per group	Additions to supplement A	Chlortetracycline addition mg /day	Average	
				Initial wt., lb.	Daily gain, lb.
56	5	Ground corn cobs	0	682	1.69
56	5	Ground corn cobs	75	680	2.18
56	5	Ground corn cobs		678	1.83
161	9	Ground corn cobs	0	713	1.26
161	9	Ground corn cobs	75	713	1.53
168	9	Ground cobs plus ground yellow corn	0	711	2.18
168	9	Ground cobs plus ground yellow corn	75	715	2.16
49	12	Green chopped corn	0	1021	2.28
49	12	Green chopped corn	75	1032	2.71

First week 25 mg., second week 50 mg., then 75 mg. daily

cycline 30 mg per lamb per day during a 117 day feeding period. Reductions in scouring and enterotoxemia were found to be associated with feeding chlortetracycline by Kunkel and co-workers[210, 211] as follows in 118 without antibiotic 8.5 per cent died of enterotoxemia and 9.3 per cent died of all causes in 232 lambs fed 5 to 15 mg of chlortetracycline per lb of diet, 1 7 died of all causes with no deaths from enterotoxemia. Enterotoxemia in lambs is commonly accompanied by clostridial infection of the digestive tract. No effects of antibiotics, chlortetracycline, oxytetracycline and penicillin, were obtained in an experiment with lambs by Kinsman and Riddell.[212] Bohman and co-workers[213] fed graded levels of chlortetracycline, 5 to 20 mg./lb of grain mix, to 140 lambs from 2 to 4 weeks of age to market weight, with or without added B vitamin No detrimental or beneficial effects were noted on rate of gain dressing percentage or carcass grade.

The experimental work with lambs indicates that a variable but predominantly favorable effect is obtained when lambs are fed a low level of chlortetracycline, about 10 mg /lb of diet. Many of the observed effects appear to be related to the suppression of harmful bacteria. High dosage with antibiotics may cause digestive disturbances. Good results have been found when antibiotics were fed to cull or scrub lambs.

The Effect of Dietary Antibiotics on Reproduction in Animals

A number of investigators have studied the results of adding antibiotics to the diet on reproduction in chickens, pigs, and, in a few cases, laboratory animals. Most of the measurable effects have been beneficial. In a number of cases, no effects were found. The interpretation of such results may be complicated if the maternal diet is inadequate with respect to certain vitamins which are spared" by an antibiotic.

Antibiotics do not readily pass through the placental barrier into the fetus as judged from studies with pigs nor do antibiotics tend to become concentrated in the egg yolk. Carpenter and Larson[214] fed 1 Gm. of chlortetracycline three times daily to sows, starting two days before the expected farrowing date. The baby pigs were bled within the first few hours after birth and before they had nursed, but no antibiotic was found in their blood serum, although it was present at levels of 0 03 to 1.3 μg /ml. in the serum of all 5 of the sows.

Various investigators have studied the birth weight and survival rate of young pigs as affected by adding antibiotics, in most cases chlortetracycline, to the maternal diet. In some of the earlier experiments, crude supplements

Table XXI

Effect of Chlortetracycline on Reproduction in Pigs

Investigators	Level of chlortetracycline Gm /ton	No of sows and gilts Started	Farrowed	Av no. pigs/litter	Av birth wt., lb.	Pigs born dead, %
Carpenter and	0 (a)	16	15	7.0	2.95	7 1
Larson[314]	20 (a)	23	17	8.3	2.98	4.8
	0 (b)	14	14	10.6	2.9	18.9
	20 (b)	14	14	8.6	3 1	5.8
Catron[197]	0	20	18	8.9	2.89	9
	40	20	19	9.7	2.84	16
	0	10	7	6.9	2.90	10
	20	11	10	6.1	2.88	5
	0	25	20	10.0	2.90	10
	40	25	19	10.3	2.86	8
	0	24	20	10.3	2.9	4
	10	24	22	10.0	3.0	11
	0	30	25	8.8	3.1	5
	10	30	26	10.6	3.0	6
Davey Green and Stevenson[318]	10 50 100	16	4 5 3	10.0 7.2 6.7	2.68 3.06 3.08	5.0 28 4.5
	10	8	3	7.0	2.66	38
	50	8	4	9.5	2.13	8.4
	100	8	7	8.7	2.51	3.4
Vestal[315]	0	13	11	8.8	2.45	6.2
	20	26	25	9.4	2.58	4.7
Beeson[317]	0	13	12	9.8	2.51	0.9
	10	13	12	9 1	2.36	2.8
	20	13	10	9.4	2.60	7.4
	30	13	12	9.4	2.82	0.9

were used which contained vitamin B_{12} as well as an antibiotic so that the effects could not be definitely attributed to the latter Carpenter[313] fed a supplement containing chlortetracycline and vitamin B_{12} for 49 to 90 days prior to parturition without observing any effect on the size of the litter the average birth weight, or the number of pigs born dead. Further studies[314] in which the supplement was fed through two gestation periods led to similar results, al though slight differences were observed in favor of the supplement (table XXI) Vestal and co-workers[315] used a similar supplement and found that the control pigs had an average birth weight of 2.45 lb as compared with 2.58 lb for the pigs from the sows that received the supplement at a level supplying 9 Gm. of chlortetracycline and 9 mg./ton of vitamin B_{12} No effects of such a supplement on the birth weights were found in studies by Dyer[316]

Beeson and co-workers[317] fed various levels of crystalline chlortetracycline to sows during gestation (table XXI) They found that heavier and stronger pigs were produced at birth when the level of chlortetracycline in the maternal diet was 20 or 30 Gm./ton than when the level was 0 or 10 Gm. The antibiotic had no effect on the number of pigs per litter The authors summarized their work as follows "Gilts fed Aureomycin at levels of 20 to 30 Gm. per ton of feed farrowed heavier and stronger pigs at birth than the gilts receiving no antibiotics or a level of 10 Gm. of Aureomycin. Aureomycin had no significant effect on the number of pigs farrowed or the weaning weight of the pigs. Pigs from the sows receiving the high level of antibiotic (30 Gm. per ton) during pregnancy were stronger and more uniform in appearance at weaning The percentage of the pigs weaned was not signficantly influenced by antibiotic feeding but was slightly higher for the high Aureomycin group."

The effect of chlortetracycline on reproduction in swine through successive reproductive cycles and generations was exhaustively studied by Davey and co-workers.[318] Diets containing relatively high levels of the antibiotic, 50 and 100 mg./lb. of feed, were included together with a lower level in order to accelerate or intensify the effects of continuous antibiotic feeding The high levels produced no adverse effects in number of pigs born per litter birth weights, or weaning weights as compared with a low level. The results by Davey and co-workers in table XXI represent experiments in consecutive years. The results in the second year were obtained with the daughters of the females used in the first year so that the effects of chlortetracycline were measured through two generations. The lower average weights of the second year pigs was stated to be probably due to the use of younger sows in the second year

The effects of antibiotics in the diet of the sow on the growth of baby pigs

are usually complicated by the fact that the young animals consume part of the mother's food, and the experimental results are difficult to evaluate.

Maddock and associates[119] found that chlortetracycline was not detectable in the blood and milk of sows receiving the antibiotic at levels up to 20 mg./lb. of diet. However when single oral doses of chlortetracycline up to 4 Gm. were given by capsule, a maximum level of 0.74 μg./ml. was found in the blood serum and 2.21 μg./ml. in the milk whey.

The effect of dietary antibiotics on the composition of hen's egg has an important bearing on any effects on hatchability or embryonic development. When any of several antibiotics were injected into eggs, the injections were well tolerated by the developing embryo (table III) at levels that far exceeded those that have been found in eggs following the administration of high levels of antibiotics to laying hens. Broquist and Kohler[41] found that no antibiotic potency was detectable in eggs laid by hens receiving a diet containing 20 or 200 Gm./ton of chlortetracycline, and only small amounts, ranging from 0.15 to 3.1 μg. per egg, were found when the antibiotic level was 2000 Gm./ton of diet. Wong and co-workers[230] were unable to detect the presence of oxytetracycline and penicillin in eggs even when the hens were fed the antibiotics at levels of 1000 Gm./ton of diet. Clearly any effects of the antibiotics on hatchability when fed at the usual levels are probably exerted indirectly rather than through their presence in the egg. This view is supported by publications which indicate that the content of certain vitamins in the egg may be increased following the feeding of antibiotics to hens. Waibel and co-workers[145] found increases in the biotin and folic acid content of egg yolks when penicillin was fed to laying hens at levels of either 5 or 200 mg./Kg. of diet. These authors suggested that the increases were due to changes in the intestinal flora brought about by the antibiotic. The basal diet was not deficient in biotin or folic acid.

The effect of certain antibiotics in increasing the hatchability of eggs laid by hens on diets deficient in vitamin B_{12} presents some unsolved problems. Several investigators have reported that this improvement in hatchability was not accompanied by an increase in the vitamin B_{12} content of the egg or that the increase in vitamin B_{12} was insufficient to account for the improvement in hatchability.[illegible] Sizemore and co-workers[illegible] reported in addition that the feeding of a supplement containing chlortetracycline to pullets during the growing period made them resistant to vitamin B_{12} deficiency of the breeder diet, measured by a depression in hatchability which could be corrected by vitamin B_{12}, and that this resistance persisted after the cessation of antibiotic feeding for a period of several months. This was further emphasized by their

later observations[42] in which the resistance continued into the second year after withdrawal of the supplement. Laying house mortality egg production, and fertility were not influenced by the growing or the breeder diets However the presence of a vitamin B_{12}-antibiotic supplement in the growing diet resulted in increased hatchability during the two year period in all four comparisons (table XXII) and the addition of chlortetracycline to the breeder diet also resulted in increased hatchability Embryonic mortality showed similar trends. The effect of the antibiotic during the laying period was beneficial and the addition of a supplement containing vitamin B_{12} and chlortetracycline to the rearing diet was followed by improvements in the subsequent reproductive performance. The authors suggested that the prolonged feeding of the antibiotic may influence the intestinal flora or may make available a nutrient to

Table XXII

Relation of Diets during Rearing Period and Laying Period to Mortality of Hens, Egg Production and Hatchability of Fertile Eggs in Rhode Island Red Hens

Series	Diet during rearing period	Mortality during 2 yr	Egg production during 2 yr	Hatchability 2d yr	Hatchability 1st & 2d yr
A	1	55 0	47 0	46.4	53.9
A	1 + A F S†	55 0	47 9	33.2	59 4
A	2	40 0	42 6	38.3	43.8
A	2 + A F S	60 0	45.6	73.6	79.2
	Average	52.5	45 8	47 9	59 1
B	1	30 8	42 1	61.3	66.8
B	1 + A F S	43 9	41 9	74.3	74.4
B	2	62.5	43 8	67.5	63.8
B	2 + A F S	47.5	45.0	71.6	73.3
	Average	46.2	43.2	68.6	69.6

Series A received no antibiotic during the two year laying period and series B received a supplement of crystalline chlortetracycline[42]

†A F S = Antibiotic vitamin B_{12} supplement in rearing diet.

increase hatchability It was not possible to explain th
of the apparent vitamin B_{12} content of the egg yolks for
when the birds received chlortetracycline even though t
eggs was higher The presence of an unidentified "hatchabi
of hens receiving an antibiotic as a supplement to a diet
B_{12} was also noted by Elam and co-workers.[33] Further
known vitamin like factor in the eggs of hens which had
supplements was provided by Slinger and co-workers[33] a
Hershberger.[34] Slinger and co-workers found that the prog
had received penicillin were 3 per cent heavier at 10 weeks
from hens without the antibiotic supplement. The chicks w
a commercial diet that was supplemented with penicillin a
Bentley and Hershberger fed an all vegetable diet to laying h
the effect of vitamin B_{12} and antibiotics in the diet of hens or
the progeny The addition of chlortetracycline or bacitracin to
hens increased the growth of the progeny on vitamin B_{12} defici
though the egg yolks, livers of the hens and the livers of the c
showed no difference in vitamin B_{12} content as determined with
leichmannii. Furthermore, feeding procaine penicillin to the hens
increase the growth of their progeny when both the hens and
received diets containing additional amounts of vitamin B_{12} The
tions again raise the possibility that a growth promoting factor
vitamin B_{12} may be stored in the egg as a result of feeding antibiot
[illegible] fed egg yolks to rats which received a basal corn soybean diet c
a [illegible] vitamin B_{12} and iodinated casein. Egg yolks from hens receivi
[illegible]tetracycline, bacitracin, or penicillin produced more rapid grow
[illegible] yolks from unsupplemented hens.

Egg Production in Poultry

[illegible] nutritional requirements of chickens and turkeys for egg produ
[illegible] some respects less critical than the requirements for hatchability
[illegible] terms this may be expressed in the statement that on certain defic
[illegible] will continue to lay eggs at a fairly goo [illegible]
[illegible] falls to extremely low levels, or in extr [illegible] the hatchabi
[illegible] at all.[36] The essential nature of certain vit [illegible] e eggs m
[illegible] folic acid, and vitamin B — or hatchability [illegible] ding rib
Under sanitary conditio [illegible] lished.
[illegible] have usually been fo [illegible] ere hens ar [illegible] high ra
e no effect [illegible] of e

duction Increases have been observed to accompany the feeding of antibiotics when the rate is depressed by certain unfavorable environmental conditions. Several investigators have noted improvements in hatchability when anti biotics were fed, and in some cases a marked increase was noted when the diet was deficient in vitamin B_1

No increase in hatchability and no consistent increase in egg production were noted when antibiotics were fed by Sunde et al,[127] although the highest egg production was in a group receiving a supplement containing chlortetra cycline. Berg and co-workers[128] found no effects on egg production or hatch ability when oxytetracycline or chlortetracycline were fed at levels rang ing from 4 to 15 mg./Kg of diet The reproductive performance of all the groups was excellent. Waibel and co-workers[145] stated without presenting data that the addition of penicillin to a diet of natural foodstuffs resulted in no measurable effect on egg production, egg weight, or hatchability over a 10 month period. The biotin and folic acid contents of the egg yolk were greater in the supplemented groups Lillie and Bird[205] found no significant effects of a supplement containing chlortetracycline on egg production or hatchability and Brown and co-workers[129] reported no effects with penicillin in a similar experiment with laying hens Other investigators who have reported that anti biotics were without effect on egg production include Petersen and Lampman[130] who used penicillin streptomycin and oxytetracycline- Halbrook and co-workers[131] who used chlortetracycline with both chickens and turkeys, Sher wood and Milby[132] who used chlortetracycline, oxytetracycline, and penicillin, Carpenter and Duckworth[133] who used chlortetracycline, Mariakulandia and co-workers[121] who used oxytetracycline and Johnson[134] who used penicillin.

Elam and co-workers[135] reported increases in egg production when anti biotics were added to the diet of pullets 10 birds were used in each group A decrease in egg production was noted in hot weather by Heywang[136] who found that the addition of 50 or 100 Gm of chlortetracycline per ton of diet helped to prevent the decrease. Balloun[137] noted that the addition of chlortetra cycline at a high level (100 Gm./ton of diet) improved egg production in pul lets which had gone into a laying slump Egg production increased from the January average of 29 4 per cent to 40 7 per cent in February in two groups where chlortetracycline was added to the diet at the rate of 100 Gm./ton. The improved rate of production was continued in March. No increase in production occurred in unsupplemented controls during the same periods.

Heywang[138] found that the addition of chlortetracycline at levels of 50 or 100 Gm./ton to the diet of laying pullets resulted in greater egg production during periods of hot weather than was observed in unsupplemented controls.

This may indicate a diminished resistance to chlortetracycline-sensitive injurious microorganisms during hot weather (average mean temperature 88 F)

White-Stevens and Zeibel[339] studied the effects of chlortetracycline during various periods of the growing period on egg production by pullets. A significant and consistent month to-month difference in egg production was found between hens receiving 50 Gm. of chlortetracycline per ton of diet throughout the growing and laying period as compared with controls. Three groups of 65 hens were used for each treatment. The per cent production (eggs per 100 hens per day) for 12 month periods was as follows there was 65 9 per cent egg production without antibiotic, 69.1 per cent when chlortetracycline was fed before egg-laying started, 67.3 per cent when chlortetracycline was fed only after egg-laying started, and 69.8 per cent when chlortetracycline was fed throughout the 12 month period. Carlson and Kohlmeyer[340] selected physically superior pullets and fed them a diet containing 50 to 100 Gm./ton of chlortetracycline, following which these birds produced more eggs than controls which had appeared to be physically superior Carlson and co-workers[341] also noted that egg production in turkeys was improved slightly when chlortetracycline was added to a diet which contained supplementary vitamin B_{12}.

Antibiotics and Egg Production in Hens with Chronic Respiratory Disease

The appearance of signs of chronic respiratory disease in laying hens is characteristically accompanied by a drop in egg production. The effect of high levels of chlortetracycline in the diet in the control of chronic respiratory disease was studied by White-Stevens and co-workers.[342] In one experiment chronic respiratory disease appeared in a breeder flock containing 296 hens that had been in production for 10 months. The flock was divided into two equal groups and one group received an addition of chlortetracycline, 100 Gm./ton of feed. At the start of the experiment the hens in the supplemented group were laying 7 4 per cent less than the controls but during the final week of the 45 day experimental period the birds receiving the antibiotic produced 7 9 per cent more eggs per hen per day than the controls. A second experiment was carried out using 630 hens per group. Levels of 0, 50, 100 and 200 Gm. of chlortetracycline per ton of feed were used. The highest level was decreased to 100 Gm./ton after five months The cumulative egg production of the first two groups was equal during a nine month period and egg production in groups 3 and 4 were respectively 8.3 and 3.3 per cent more than the control group. The hatchability for group 1 was 79.0 per cent, for group 2, 83.4 per

cent for group 3, 83.3 per cent and for group 4 83.1 per cent, so that the combined effects of increased egg production and hatchability were in favor of the supplemented groups. Carson and co-workers[343] found that egg production in pullets with CRD was improved by injecting a suspension of 50 mg of oxytetracycline in mineral oil. The mean egg production of 143 treated birds for 81 days of the postinjection period was 44.7 eggs as compared with 38.6 eggs for the control birds.

The effect of chlortetracycline on the egg production by turkeys in flocks where sinusitis and bluecomb were occasionally observed was improved by chlortetracycline. The average egg production in two unsupplemented groups totaling 593 birds was 45 and 55 per cent. The production of two corresponding groups receiving 115 Gm./ton of chlortetracycline was 57 and 58 per cent and for two groups with 230 Gm./ton of chlortetracycline, 59 and 61 per cent.[342]

CHAPTER V Physiologic and Other Effects Of Dietary Antibiotics

Effects of Antibiotics on the Endocrine System

Chlortetracycline and the Thyroid Gland. Ershoff has reported[244, 245] that crude supplements derived from the fermentation of penicillin or chlortetracycline prolonged the survival of immature rats which received toxic doses of desiccated thyroid gland. He noted that crystalline chlortetracycline hydrochloride was ineffective thus perhaps indicating the existence of an unidentified nonantibiotic factor in the residues However Meites and Ogle[246] found that penicillin and neomycin were effective in overcoming the growth-depressing effect of iodinated casein for rats. No goitrogenic effects were observed for the antibiotics. Calesnick and co-workers[247] reported that either penicillin or chlortetracycline at the low level of 1 mg /Kg of diet produced a severalfold increase in the weight of thyroid glands of immature white rats with a three-to-fourfold decrease in I^{131} uptake by the gland after 42 days of feeding They suggested that chlortetracycline and penicillin had a goitrogenic action similar to the thiouracils. Inability to repeat these observations was reported by Libby and Meites[248] and by Grant.[249] In studies with rats, even though 20 to 50 times higher levels of the antibiotic were fed than were used by Calesnick, Grant noted in contrast that there was a small but definite increase in the uptake of I^{131} by the thyroid when chlortetracycline was fed to rats. It was also pointed out by Grant that rats receiving 2 per cent propylthiouracil in the diet as used by Calesnick and co-workers lived for less than two weeks in his experiments as opposed to the results reported by Calesnick et al who indicated that their rats lived through the six week period on the propylthiouracil supplement.

No effect on the iodine metabolism of thyroid slices in vitro was found in experiments with chlortetracycline by Taurog and Chaikoff.[250] These investi

gators incubated sheep thyroid tissue slices in Ringer solution containing
with or without 10 μg./ml. of chlortetracycline. After two hours of incub
at 37 C the tissues were homogenized and hydrolyzed with pancreatin an
hydrolysate was chromatographed for separation of the iodine-containing
tions. The chromatograph indicated that both preparations contained app
mately the same amounts of radioactive diiodotyrosine, monoiodotyrosine,
roxine, and free iodide so that chlortetracycline had no effect upon the up
of I^{131} or on organic I^{131} formation by sheep thyroid tissue slices. Their find
indicate that any effect of dietary antibiotics on the thyroid is indirect, per
mediated through the intestinal bacteria.

Similarly Telkkä and Kuusisto[351] found no differences in the histol
picture of the thyroid gland of antibiotic-supplemented rats as compared
the controls. Both chlortetracycline and oxytetracycline were used at level
10 mg./Kg. of diet. The relative weight of the gland was practically the
in all three groups. Maghrabi and Turner[352] noted a slight depression of thy
size in young chicks that received 50 mg. of chlortetracycline per Kg. of
A small increase in the weights of the thyroid glands of chicks recei
chlortetracycline was noted at eight weeks of age by Mellen and Walle
The thyroid weight was 67 mg./Kg. of body weight for the unsupplemen
birds, 83 mg. for the chlortetracycline-fed birds, and 76 mg. for the birds
ceiving bacitracin. No such differences were found by Grant[354] as shown
table XXIII.

Both chlortetracycline and vitamin B_{12} were reported by Meites[355, 35
counteract the deleterious effects of cortisone on vitamin B_{12}-deficient
The effect of the antibiotic would seem to be related to improving the util

Table XXIII

Average Body Weights, Thyroid Weights, and I^{131} Uptake of 10 Week Old Male Chickens 24 Hours after Intravenous Injection of I^{131}

Chlortetracycline added per ton of diet	Body wt., Gm.	Thyroid wt. mg./Kg. body wt.	I^{131} uptake C.P.M. per mg thyroid
None	1259	90.1	158
100 Gm	1359	89.4	156

*There were 10 birds per group.[354]

Table XXIV

Partial Protection of Rats Against Alloxan Diabetes by Chlortetracycline

Treatment	Chlortetra cyclin per Kg of diet Gm	Av gain in body wt in 28 days Gm.	Average daily Diuresis, ml.	Average daily Urinary sugar Gm.
None	0	28		
None	0.2	28		
Alloxan	0	9.6	73	3.85
Alloxan	0.2	19.0	88	5.0

tion of vitamin B_{12} or increasing its intestinal synthesis Wahlstrom and Johnson[199] found that cortisone aggravated vitamin B_{12} deficiency in baby pigs but no alleviation was produced by chlortetracycline.

An effect of chlortetracycline on partially protecting rats against alloxan diabetes was reported[197] and is summarized in table XXIV

The experiment was carried out because it had been observed that patients with severe diabetes had shown improvement during treatment with chlortetracycline.

The effects of chlortetracycline singly and in combination with diethylstilbestrol and L-thyroxine on the growth of pigs were studied by Barber and coworkers[238] who found evidence for an additive effect on growth and feed efficiency when the combination was fed.

Effects Following Various "Stress" Conditions Baez et al[239] found an 18 per cent greater survival after rotation in a drum in rats receiving oral chlortetracycline than in untreated controls These results prompted an examination of the liver slices of the experimental rats, and it was found that the liver preparations from rats receiving chlortetracycline orally or via portal vein injection did not release vasoactive ferritin (VDM) into the incubation medium after 90 and 120 minutes of anoxia, in contrast to control liver slices. This suggested a mechanism by which chlortetracycline may have partially protected the drummed rats against shock. Fine[240] reported that penicillin and chlortetracycline were ineffective when administered parenterally in prevent

ing irreversible shock induced by hemorrhage in dogs, but these antibiot together with neomycin produced a resistance to shock when given by mou

Chlortetracycline and streptomycin at levels of 50 mg/Kg. of diet w found to increase the tolerance to emetine in rats on a low protein diet.[341]

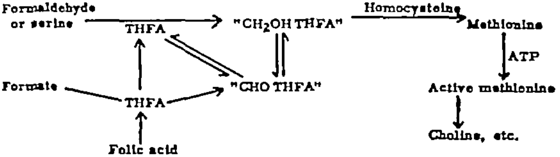
Radiation Injury Following exposure of the total body to roentgen ra acute radiation sickness, accompanied by hemorrhage and infection, may d velop. A number of investigations have shown that protective effects may times result if antibiotics are administered to experimental animals prior irradiation. Such effects may be important in the event of accidental expos to radioactive materials. Penicillin, streptomycin, chlortetracycline, and o tetracycline have all been used in these experiments.

Howland and co-workers[342] found that chlortetracycline alleviated diarrh and prolonged the survival time for five to seven days beyond the contr in rats following an LD_{90} dose of roentgen ray radiation. Chloramphenic streptomycin, and penicillin were less effective. Good results were also obtain with chlortetracycline in dogs Miller and associates[343] found that the mo tality of irradiated mice was lowered by streptomycin and to a lesser degr by chlortetracycline but that the protection was less if the mice develop certain infections Gustafson and Koletsky[344] reported that oxytetracycli probably protected against radiation injury by reducing bacteremia, in an e periment in which oxytetracycline was given 72 hours prior to radiation, t mean survival time was raised to 15 0 days from 10 6 days.

In further studies by Furth and his associates[345-347] the results with do and rats were indefinite. In two experiments, each involving 96 dogs, n protective effects were obtained from either chlortetracycline or whole bloo transfusions The authors nevertheless concluded[347] that "the prophylact administration of a broad spectrum antibiotic is still advisable despite th results of this study" in the event of an atomic catastrophe and the conseque exposure to infection.

Antibiotics and Liver Physiology

Antibiotics and Deficiencies of Choline and Methionine. Deficiencies folic acid and vitamin B_{12} are well known to lead to increase the disturbanc arising from dietary deficiencies of choline and methionine in the diets of ra and chicks. Folic acid has a coenzymatic role via tetrahydrofolic acid (THF and its derivatives in the synthesis of methionine from homocysteine and "single-carbon unit," which may be derived from formaldehyde, serine, formate as follows[348, 349]



The role of vitamin B_{12} is not clear but it seems to be connected with the formation or utilization of CH_2OHTHFA, the hydroxymethylated coenzyme that is involved in one route for the formation of methionine from homocysteine. The second route for this synthesis is through the combination of betaine or dimethylthetin with homocysteine in the presence of transmethylase. If the utilization or intestinal synthesis of folic acid and vitamin B_{12} is improved by adding antibiotics to deficient diets, the effects of deficiencies of choline or methionine such as fatty livers, hemorrhagic kidneys, or necrotic livers, may be alleviated[370] and anti-anemia effects of the antibiotic may also be shown.

Hepatic necrosis, a dietary liver disease of rats, has been extensively studied by Gyorgy and co-workers who showed that it was possible to produce the disease on a diet high in yeast and to prevent it by adding vitamin E, cystine or methionine. Chlortetracycline was also found to prevent hepatic necrosis when added to the diet of rats[46] but in contrast to the other preventive agents the effect of chlortetracycline was found to be only temporary. The mechanism for this effect of the antibiotic was thought to be an inhibition of toxin-producing bacteria in the lower intestine because the necrosis developed predominantly in the left lobe of the liver which derives its portal blood from the large intestine and stomach in contrast to the relatively normal right lobe which receives portal blood from the small intestine. Abell and Beveridge[371] confirmed the results with chlortetracycline and found that sulfaguanidine had some protective action. A number of antimicrobial agents were tested[372] and chlortetracycline was found to give the longest protection, followed by oxytetracycline and streptomycin, then by sulfaguanidine while chloramphenicol, polymyxin, and penicillin were ineffective. Vitamin B_{12} had no effect. The temporary nature of the protection given by chlortetracycline led to the conclusion that its effect was not direct but was mediated through a transient change in the intestinal flora and that eventually the bacterial

types that were postulated as producing hepatotoncosis reappeared in an antibiotic-tolerant form. In later studies penicillin was found to be effective.[373] The intestinal flora of the experimental rats on penicillin and chlortetracycline supplements was studied and the type of changes produced by the two antibiotics differed, furthermore, resistant bacteria appeared in the first week while the antinecrogenic effect lasted for five or six months.[374]

Against the bacterial theory of hepatic necrogenesis were observations with germ-free rats[375] which developed the disease when on a restricted food intake but not when on full feed. This makes it appear that some ingredient *of the deficient diet could* prevent necrosis and *that the ingredient*, perhaps methionine or cystine, was absorbed in sufficient amounts only when the animals were on full feed under the germ-free or antibiotic-supplemented conditions both of which have been reported to be accompanied by certain changes in the intestinal wall.[64] The addition of antibiotics produced a change in the pattern of the urinary excretion of ether-soluble acids as compared with unsupplemented or vitamin E-treated animals.[376] Two unidentified acids with R values of 0.45 and 0.80 in butanol-acetic acid water mixtures appeared in the urines of the antibiotic-supplemented rats, these substances had no apparent relation to necrogenesis but their presence may be of much biochemical interest. The urinary *excretion of volatile* phenolic compounds by human subjects was found to decrease markedly following the administration of antibiotics by mouth. This was thought to be due to a depression of the bacterial formation of phenols from tyrosine in the intestinal tract.[377]

In other experiments by Gyorgy and his collaborators,[372] rats were fed an entirely different diet, deficient in labile methyl and containing sucrose, 88 per cent lard, and 8 per cent casein, which produced cirrhotic changes and kidney injury *The changes were prevented by chlortetracycline*, 25 mg *daily*[372] *These findings with rats may be compared with clinical* investigations in which chlortetracycline was used in the treatment of hepatitis,[378, 379] hepatic coma,[380] and cirrhosis.[381, 382] A patient with chronic posthepatitic cirrhosis and continuous jaundice of four years duration showed striking improvements, including histopathologic changes, following five months intensive treatment with chlortetracycline.[381] Three patients with acute fulminating hepatitis recovered following treatment with chlortetracycline.[379] *However in* a controlled study[378] no difference in the course of acute viral hepatitis was found between chlortetracycline-treated and control patients when 87 cases were studied in each group De la Huerga and co-workers[383] reported that dietary chlortetracycline, oxytetracycline, and penicillin suppressed the urinary excretion of trimethylamine in dogs following the ingestion of a test dose of choline. This

effect was thought to be due to the lowering of trimethylamine formation by the intestinal bacteria. The effect disappeared after one or two weeks as if the bacteria had become adapted to the presence of the antibiotic. However Kaplan and co-workers[384] were unable to repeat these observations They found that chlortetracycline had a lipotropic effect on dogs with ligated pancreatic ducts when given in large doses. Similar changes occurred when choline was administered. The effects produced by chlortetracycline reached a maximum in three to four weeks and then receded and leveled off at an intermediate level, in one animal a second response was produced by adding folic acid and vitamin B_{12} to the treatment with chlortetracycline Either choline or chlortetracycline were found by Baxter and Campbell[385] to prevent renal lesions in rats on diets high in fat and low in choline. Vitamin B_{12} had some activity but oxytetracycline, chloramphenicol, and penicillin were ineffective. No change in the liver lipids of rats was produced by adding chlortetracycline to a low protein, low fat diet in studies by Cornatzer and Gallo[386] and after four weeks there was a decrease in phospholipid synthesis in the group fed chlortetracycline. On the clinical side, 12 cases of chronic liver disease were treated with chlortetracycline, 7 of whom showed an improvement while in the remaining 5 cases there was little or no evidence of benefit.[387]

These effects of antibiotics may be contrasted with the findings of Seto and Lepper[388] who found that an increase in the liver fat of young female rats was produced by a single intravenous injection of chlortetracycline or oxytetracycline, 100 or 150 mg /Kg of body weight as follows the per cent liver fat, 18 to 24 hours after injection of the chlortetracycline was 15.5 ±5.4 and the control was 7.1 ±1 6 the per cent liver fat, 18 to 24 hours after injection of oxytetracycline, was 13.5 ±6.2, and the control was 6 0 ±1.8.

The liver fat values returned to normal within three days following withdrawal of the drugs. No change in the effect was noted when methionine or various B vitamins were given simultaneously The experimental intravenous route of administration may have been the reason for the difference between these results and those previously described,[372, 384] and it is interesting to note that Zimmerman and Humoller[389] found that oral chlortetracycline did not effect the endogenous respiration and choline oxidase activity of rat liver tissues while chlortetracycline given parenterally or added in vitro depressed these systems However Sborov and Sutherland[390] found that treatment with chlortetracycline, 2 Gm. daily by mouth in a group of 16 patients with chronic viral hepatitis or hepatic cirrhosis, was followed by increased liver fat as indicated by biopsy These patients received a diet which averaged 126 Gm. of fat daily so that the increases in liver fat were perhaps to be expected, moreover

toxic properties. Bacitracin may produce renal tubular necrosis, especially i mice Neither streptomycin nor bacitracin are readily absorbed from the di gestive tract when given orally

Massive doses of chlortetracycline were given to pigs by Cameron[409] wh found no toxic effects when 250 mg./Kg of body weight was fed daily for 2 days. The level of the antibiotic normally consumed by pigs receiving typica chlortetracycline-supplemented feeds would not exceed 1 mg./Kg. of bod weight daily The pigs were in excellent condition at the end of the experimen and the bone marrow was found to be yellow in color at autopsy but showe no histologic abnormality

Effects on Growth of Human Subjects

An approach to the study of the effects of antibiotics on the growth of children presents certain difficulties as compared with experiments with ani mals, first, because every effort must be made with children to exclude the bacterial contaminations that contribute so much to the antibiotic growth effect in animals and, second, because of the slow rate of growth of human beings. The most marked effects of antibiotics on the growth of children may be expected where they are poorly developed due to subnormal diets or to subacute intestinal diseases

Several encouraging reports have appeared regarding premature infants. Perrini[410] fed chlortetracycline, 25 mg./Kg. of body weight daily to 10 premature infants and found that they gained 8 per cent in weight during a 10 day period as compared with no weight increase for a group of 23 controls. Robinson[411] also reported increased growth with premature infants receiving chlortetracycline who gained 29.5 Gm. daily as compared with controls who gained 18 Gm. daily Five of the 15 controls died from intercurrent infections while all of the supplemented group lived. Lower mortality in a group of chlortetracycline-treated premature infants together with increased growth was reported by Snelling and Johnson [412] there was one death in a group of 47 who received 50 mg of chlortetracycline daily as compared with 8 deaths in 48 controls In a study of 57 supplemented premature infants and 56 controls, Coodin[413] found that oxytetracycline, 25 mg daily failed to alter the rate of weight gain The mortality rates were not reported. No effects in increasing weight gains were found in 2 infants studied by Kaye et al.[414]

Growth increasing effects for antibiotics on infants were reported by Déchêne[415] and Wetzel and Hopwood,[416] who found that oxytetracycline, streptomycin, and penicillin, 10 to 50 mg daily by mouth, improved the

growth of school children Scrimshaw et al[417] studied Mayan children 7 to 12 years of age living in the Guatemalan highlands and subsisting on diets low in animal protein. In one experiment, 14 children who received 50 mg. of chlor tetracycline daily for 15 months gained an average of 0 48 cm. of height monthly as compared with 0.33 cm. for 43 control children In two successive 12 month periods following withdrawal of the antibiotic, they had the same rate of height increase as control groups. In other experiments the increases in height are shown in table XXV The average monthly weight gains varied widely irrespective of the type of treatment. It was concluded that the oral administration of chlortetracycline daily stimulated growth in stature in primary school children under the experimental conditions encountered but the response to penicillin was variable

Carter[418] carried out a prolonged investigation of a study of the effects of administering 75 mg of chlortetracycline twice daily to mentally defective children for periods up to three years at the Florida Farm Colony The children were mentally deficient spastic cases and were almost entirely helpless The average yearly gain in weight for the supplemented group was 6.5 lb while the control group averaged 1.9 lb in yearly weight gain. The supplemented group had a lower incidence of gastrointestinal disorders than the controls.

The effect of chlortetracycline on weight gains of undernourished children in Kenya was studied by Macdougall.[419] Thirteen children in the age range of 1 to 3 years received chlortetracycline, 50 mg daily for one to seven weeks and

Table XXV

Increases in Height of Children with and without Antibiotics

		Monthly gains in height cm.*		
Experiment	Length of time	Controls	50 mg penicillin	50 mg. chlortetracycline
1	15 months	0.33 (43)		0.48 (14)
2	18 months	0 43 (23)	0 41 (32)	
3	5 months	0.35 (38)	0.36 (38)	0.44 (35)
4	5 months	0 43 (35)	0.51 (39)	0.50 (37)

The number of children per group is given in parentheses.

The prolonged feeding of comparatively high levels of the common antibiotics to animals has not raised problems in public health as regards the consumption of animal products. Broquist and Kohler[41] found no detectable amounts of chlortetracycline in the liver and muscle of chicks receiving chlortetracycline, 200 mg./Kg of diet. Barely detectable amounts were present in the blood serum. At unusually high dietary levels, traces of the antibiotic were found in the liver and muscle. The values ranged from less than 0.05 to 0.165 µg./Gm. of muscle when the diet contained 2 Gm./Kg of chlortetracycline up to 0.18 to 0.39 µg./Kg of liver with 6 Gm. of chlortetracycline per Kg of diet. Similarly with pigs the level in the muscle tissue was 0.30 µg./Gm. with 2 Gm. of chlortetracycline per Kg. of diet and undetectable in the muscle with 200 mg./Kg of diet. In further studies, Kohler and co-workers[127] found that chlortetracycline in poultry meat was readily destroyed by cooking and the destruction of chlortetracycline proceeded more rapidly than that of oxytetracycline. Chicken breast muscle containing 3 µg./Gm. of chlortetracycline was found to be free from the antibiotic after boiling for 15 minutes or after roasting for 30 minutes at 230 C.

The prolonged administration of chlortetracycline to human subjects has not produced untoward effects. A group of 184 elderly patients were dosed orally with 500 mg of chlortetracycline daily for prolonged periods in a study by McVay and Sprunt and an equal number in a control group received placebos.[128] In the groups with congestive heart failure, there were 15 deaths in the chlortetracycline group who were medicated for 20 months and a decrease in the incidence of respiratory infections in 30 patients as compared with 19 deaths in the control group and a decrease in respiratory infections in 4 control patients. Hematocrit values were higher in the chlortetracycline group. Along similar lines 169 diabetics were observed for an average of 19.5 months, again with a decrease in respiratory infections in the chlortetracycline group. Comprehensive liver function studies showed some evidence of improvement in this group. These observations emphasize the lack of toxicity of chlortetracycline when administered for prolonged periods at high dosage rates. No toxic reactions are imaginable from the traces of chlortetracycline which might be present in the meat of animals fed high levels of the antibiotic. Indeed, these traces of antibiotic were only of the order of 50 µg./lb. or less of muscle tissue even when the chickens received 2000 Gm. of chlortetracycline per ton of diet[41] and the antibiotic was destroyed by ordinary cooking procedures. It

is also worth noting that the antibiotic-tolerant strains of bacteria, which appear in the intestinal tracts of animals receiving dietary antibiotics appear not to be pathogenic· the report of Libby and Schaible[183] indicates a downward trend in the mortality of chickens during four years of feeding antibiotics. Markham and co-workers[139] found that the feeding of high levels of chlortetracycline did not inhibit the development of a normal immune response to vaccination for Newcastle disease and infectious bronchitis in chicks.

Conclusions

An apparent improvement in the nutritional status of animals may be often produced by adding small quantities of certain antibiotics to the diet. The utilization of food is often increased in growing animals by this addition as measured by a consequent decrease in the amount of food required to produce a unit of gain in body weight. The daily rate of gain in weight is increased and the percentage of unthrifty animals is reduced. These effects are of great economic and practical importance in agriculture. Many experimental investigations of the nutritional changes underlying these effects have been made and a sparing action of antibiotics on the requirement for certain nutrients has often been noted.

The mechanism by which the antibiotics produce their effects on nutrition appears to be secondary to their antibacterial action. Variations in the extent of these effects are inevitable in view of the inherent variations in the bacterial population. Changes presumably take place in the intestinal bacteria and these changes are responsible for the nutritional effects. Examinations of the types of bacteria in the intestinal contents of antibiotic-fed animals have led to variable and inconclusive findings as regards any correlation between feeding antibiotics and the establishment of specific bacterial types When antibiotics are administered, the total numbers of bacteria in samples of the intestinal contents characteristically decrease for a few days and then increase above the original levels. Perhaps antibiotics suppress certain bacterial forms which are inhibitory not only to the growth of the host but also to the growth of some of the other intestinal bacteria

The prolonged and widespread feeding of antibiotics to farm animals has not led to deleterious results or to the establishment of resistant strains of pathogenic bacteria. There is much evidence which indicates that one of the results is that the premises may become cleaned up so that the growth of the resident animals is improved even in the case of those animals on the same premises which are given unsupplemented diets

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